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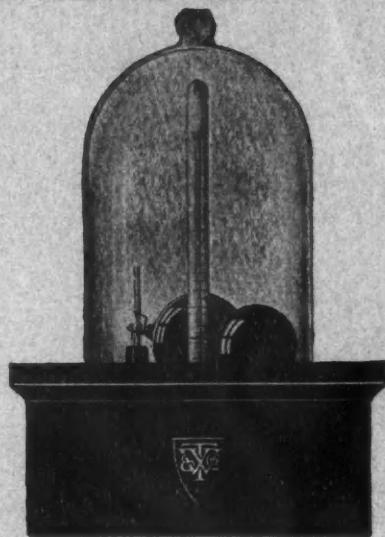


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The Preparation of a Scarlet Fever Streptococcus Toxoid and its Use in Active Immunization*

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A SUFFICIENT number of investigators have demonstrated that the toxin produced by the hemolytic streptococcus of scarlet fever origin can be detoxified, at least in part, by the action of formalin and prolonged storage at 37°C., so that this procedure may be accepted as within the realm of possibility. However, there remain to be solved such problems as (a) the most practicable method of manufacture; (b) laboratory methods of titrating the antigenic value of this detoxified product; (c) the range of doses tolerated by susceptible individuals without undue reactions; and (d) the immunity response of susceptible individuals as indicated by the percentage who become Dick negative subsequent to treatment. The study which is presented in the following pages was pursued in an effort to solve some of these problems and thereby to place the manufacture and use of scarlet fever toxoid on a practical basis.

PREPARATION OF THE TOXIN

Culture Medium

Because of the uniformly good growth and toxin production obtained with a modification of Douglas tryptic digest broth, this medium has been used exclusively throughout this study.

The basic formula for the preparation of the pancreatic extract used in this broth is given by Cole and Onslow¹ and that for the broth by Watson and Wallace². Either beef or veal may be used. Instead of using 90 cc. of concentrated hydrochloric acid to 7 kilograms of meat as directed, only 45 cc. are added. The reaction is so adjusted before sterilization as to give a pH of 7.6 in the completed broth. Blood is not added.

Full strength broth prepared in this manner contains between 300 and 400 milligrams of total nitrogen per 100 cc. This represents a food content probably far in excess of the requirements of the hemolytic streptococcus. Flasks containing 25, 50, 75 and 100 per cent broth, respectively, were inoculated and incubated for 3 days. The toxin content of the four batches after incubation was the same, as indicated by human skin tests. It is highly desirable to keep the protein content near the minimum consistent with maximum toxin production because of the possible connection between such foreign protein and reactions in the individual receiving the injection.

In the beginning of this study 75 per cent Douglas broth was used but, towards the latter part, this was changed to half-strength broth.

*Presented at the Christmas meeting of the Laboratory Section, Canadian Public Health Association, Toronto, December, 1932.

Culture

In selecting a culture of hemolytic streptococcus suitable for toxin production, one should make the selection on the basis of certain definite requirements, namely, (a) the production of a high titre toxin, (b) the resulting toxin should be neutralizable by a known hemolytic streptococcus antitoxin of scarlet fever origin, and (c) the toxin when used as an antigen should stimulate the production of an antitoxin which in turn will neutralize the greatest possible range of hemolytic streptococcus toxins. If this wide neutralization range in an antitoxin cannot be obtained by the use of a single strain antigen, the antigen from one or more additional strains should be added. However, probably nothing is accomplished by using a multiple strain antigen for antitoxin production, provided the resulting antitoxins, when the antigens are used separately, neutralize within the same range.

The NY-5 strain has been used exclusively because of the hemolytic streptococcus strains available this one more nearly meets the above criteria.

The particular culture used has been carried in broth medium with transfers every second or third day and kept continuously at 37°C. since October, 1929, without animal passage. Wheeler³ states that of 500 strains studied the NY-5 strain proved of exceptionally broad valence and good toxin production. She selected eight representative strains out of these 500 and observed their antigenic activities. No strain exceeded NY-5 and only one equalled it. Coburn and Pauli⁴ report on ten toxin-producing strains of hemolytic streptococci which had been isolated from patients suffering with rheumatic fever. The toxins derived from six of these ten strains were neutralized by NY-5 antitoxin. Veldee⁵ studied commercial antitoxins and found that those which had been prepared from a NY-5 containing antigen possessed greater neutralizing properties. Veldee and Dunnahoo (unpublished data) have observed that NY-5 antitoxin neutralizes toxins derived from hemolytic streptococci from erysipelas sources as readily as do erysipelas antitoxins.

In spite of this apparent superiority of the NY-5 strain over other known strains, the search for a more suitable strain, or strains, which will fill in where the NY-5 strain fails, should continue. However, when multiple strains are used for toxoid production, the toxins should be separately prepared and detoxified and later combined on the basis of individual antigenic value.

The inoculated broth is held at 37°C. for 72 hours for toxin production. Longer periods are objectionable because of the probability of unnecessarily increasing the amount of dissolved bacterial protein. Practically all of the streptococcus growth takes place within the first 24 hours of incubation. Flasks A, B and C of broth were each inoculated with the D-II strain of hemolytic streptococcus and placed at 37°C. After 24, 48 and 72 hours, respectively, the contents of each flask were filtered through a Berkefeld and then reinoculated with the same strain of streptococcus. A scarcely visible growth appeared in the 24-hour flask, and none in the other two. Similar results were obtained with the NY-5 strain.

Correspondingly, all toxin production takes place within the first 24 hours. Eight hundred cubic centimetres of broth were inoculated with a NY-5 culture and incubated at 37°C. At the end of each successive 24-hour period thereafter, 100 cubic centimetres were removed from the flask and filtered. Subsequent skin tests on susceptible individuals showed no significant differences between the toxin content of the eight 100 cubic centimetres batches thus obtained.

Concentration of the Toxin

The quantity of antigen in the form of toxoid which is tolerated by a susceptible individual is sufficiently large to make concentration highly desirable, if not essential. In a previous paper (*loc. cit.*) a method of concentrating the toxin was described which employed precipitation with acetone and acetic acid. The method represented a modification of a method described by Wadsworth and Quigley⁶. It gave a highly purified toxin as measured by the small amount of total nitrogen in the finished product, but subsequent experience has shown that such a concentrate seems to lack stability and results in a very considerable loss of toxin. Further, such a highly purified product is not essential in the preparation of a toxoid.

Because of these objections the concentration method used has been simplified to the following. Two volumes of acetone and one volume of toxin are cooled to 0°C. (if facilities are available it is well to cool the acetone even further). The toxin is added to the acetone and thoroughly mixed by rotating the flask vigorously for three to five minutes (violent shaking is not desirable), after which it is allowed to remain in the cold room until the flocculent precipitate has settled to the bottom (approximately one-half to one hour). The precipitate is collected in a Buchner funnel by means of suction filtration. By placing a thin layer of paper pulp over the filter paper in the funnel the small holes do not become plugged and filtration proceeds rapidly. Suction is continued until all the acetone has been removed from the precipitate, after which the precipitate, paper pulp and filter paper are placed in a volume of normal saline equivalent to one-tenth the volume of the raw toxin used. Gentle stirring, to avoid foam, or allowing to stand in the cold room over night will cause the precipitate to redissolve. A second filtration through a Buchner removes the paper pulp and filter paper. To this filtrate is added sufficient full strength broth to make the final volume one-fifth the volume of the raw toxin used in the beginning. The reaction is adjusted to pH 7.4 and as a last step the concentrated toxin is filtered through a Berkefeld candle.

The end results obtained by this method of concentration are shown in table 1, where there is also a comparison with five lots of unconcentrated commercial toxins which were offered for purposes of active immunization by the Dick method. Those concentrates designated by the letters "WA" were prepared by precipitating both with acetone and acetic acid, whereas the two marked "W" were prepared by the method described above. The "WA" toxins have been concentrated ten times by volume as against five times concentration of the "W" toxins, yet each batch contains approximately the same total nitrogen and potency. The use of acetic acid removes more of the nitrogen-containing ingredients, but its use also causes a very great loss of toxin. With the use of a half-strength broth for toxin production and by concentrating five times by volume with the acetone method, as was done with toxins HL-32W and HL-34W, a final product is obtained whose nitrogen content is no greater than unconcentrated toxin made from full strength broth and whose potency is three and one-half to four times that of a good unconcentrated toxin.

Little was known of the chemical nature of the toxin and of its behavior under various conditions, particularly if removed from its original broth environment. It was known that this toxin could be changed to toxoid by the action of formalin without the loss of much of its antigenic value when retained in the original toxin broth and, therefore, it seemed advisable to retain the concentrated toxin in a menstruum which would be very similar to the original broth. This reasoning has been fortified by the subsequent publication by Bunney⁷ of his study on the action of formalin on diphtheria toxin in various stages of purification.

Experiments with detoxification of the toxin before concentration are under way. Should this procedure prove practicable, it would eliminate the need for re-solution in broth and thus reduce the total nitrogen content of the concentrated toxoid by one-half as compared to the method just described.

PREPARATION OF THE TOXOID

Method of Detoxifying

The practice has been to add 0.4 per cent formalin to the concentrated toxin and store at 37°C. On the following day the reaction is adjusted to pH 7.2 by the addition of a solution of sodium carbonate. Skin tests for toxicity are made on the ears of susceptible white rabbits at the end of about

60 days. If considerable toxicity still remains, an additional 0.05 per cent of formalin is added and the pH adjusted as above. The toxoid is allowed to remain in the warm room until tests indicate that the residual skin reacting factor is not greater than 500 skin test doses per cubic centimetre, which represents a reduction of more than 99.5 per cent in the skin reacting factor of a toxoid considered suitable for immunization purposes (see tables 1, 2 and 3). Table 2 indicates that this was accomplished in 56 to 88 days with toxoids Td-11, Td-12, Td-16, Td-20 and Td-21. The skin reacting factor in Td-21 was reduced from approximately 175,000 STD per cubic centimetre to 500 in 66 days. Leaving it in storage for another 39 days only reduced the skin reacting factor to 400 STD per cubic centimetre. Toxoid Td-14 still contained a residual of 1,500 STD after 82 days' storage. This lot contained a total of 526.5 mgm. of nitrogen per 100 cc. (table 1) as against 190.4, 270.0, 323.7 and 323.7 and 317.4 mgm., respectively, for the above toxoids. The rate of detoxification is influenced by the concentration of formalin and the total nitrogen content of the toxin. There appears to be an irreducible minimum of skin reacting factor which cannot be detoxified. It is not entirely clear whether this is true toxin or some other substance.

TABLE 1. The total nitrogen and the estimated potency of certain concentrated scarlet fever toxins used for the manufacture of toxoid, as compared to the total nitrogen and potency of certain market samples of commercial toxins.

A. National Institute of Health concentrated toxins.

Designation of toxin	Concentration by volume	Total nitrogen expressed as milligrams per 100 cc.	Estimated potency expressed as skin test doses per cc.
1930	unconcentrated	326.0	50,000
HL23WA	2 times	190.4	75,000
HL25WA	10 "	270.0	200,000
HL26WA	10 "	374.3	200,000
HL27WA	10 "	526.5	200,000
HL32W	5 "	322.3	175,000
HL34W	5 "	317.4	175,000

B. Commercial unconcentrated toxins.

Laboratory A	unconcentrated	347.6	45,000
" A	"	370.1	35,000
" D	"	394.6	60,000
" E	"	249.3	40,000
" F	"	446.6	50,000

Heat Stability of Toxin and Toxoid

The original unconcentrated toxin which has been used in this study contained 45,000 STD per cubic centimetre. Subjecting this toxin to streaming steam in the Arnold sterilizer (approx. 99°C.) for varying lengths of time caused the following reductions in the titre of the skin reacting factor:

Period of exposure to streaming steam	Titre of the heated toxin in terms of skin test doses as compared to the reaction pro- duced by 1 STD of standard control toxin	
	less than	at least as much as
Before heating		45,000 STD per cc.
30 minutes	25,000 STD per cc.	10,000 " "
60 "	10,000 " " "	5,000 " " "
120 "	5,000 " " "	2,000 " " "
180 "	1,000 " " "	100 " " "
240 "	100 " " "	10 " " "

From these data it would appear that the skin reacting factor is heat labile within the limits described for this test and that the rate of destruction proceeds in an orderly manner.

A concentrated toxin (Toxin HL-32W, which became toxoid Td-16 after detoxification) was similarly heated for 60 minutes. This reduced the skin reacting factor from 175,000 STD to approximately 25,000 STD per cubic centimetre, which is an 85.7 per cent reduction as compared with an approximate 88.9 per cent reduction obtained with the unconcentrated toxin in the same length of time. Similar heating of the toxoid Td-16 reduced the residual skin reacting factor from the equivalent of 500 STD in the unheated toxoid down to 125 STD, a reduction of 75 per cent. The residual skin reacting factor in the toxoid appears somewhat more resistant to prolonged heating than the raw toxin. The much greater concentration of heated toxoid which must be injected for the skin test may be a factor, and the presence of bacterial proteins must also be considered.

The question now naturally arises as to whether the skin reacting factor at these various stages of heating is neutralizable with antitoxin, and, if so, how much antitoxin is required as compared with the neutralization of standard control toxin. The standard toxin and anti-toxin provided by the National Institute of Health are standardized that, on the average, one STD of toxin will be neutralized by 0.02 unit (one neutralizing skin test dose) of antitoxin. The ratio is somewhat different when tested by the rabbit ear method. Neutralization tests with standard toxin and antitoxin on 128 suitable rabbits showed that 25 STD of toxin required on an average .081 units (4.05 neutralizing skin test doses), which means that antitoxin is 6.17 times more effective in neutralizing toxin by the rabbit ear method than in the human skin. Neutralization according to the same ratio takes place with the toxin concentrated by the acetone method.

Tests on rabbits indicate that the skin reacting factor still present in unconcentrated toxin after heating in streaming steam for 60 minutes may be neutralized by antitoxin, the ratio of toxin to antitoxin being the same as with the unheated product.

The residual skin reacting factor remaining in the toxoid after detoxification, as well as that residual remaining after heating the toxoid for 60 minutes in streaming steam, can also be neutralized with antitoxin. However, the quantity of antitoxin required was in each instance much greater than for the neutralization of the skin reacting factor present in the original untreated toxin. The greater concentration of reagents required for the neutralization tests with the residual in the toxoid may be a factor.

Attempts were made to demonstrate the combining power of the toxoid with antitoxin but all tests ended in failure.

Antigenic Tests on White Rabbits

A laboratory method for measuring the antigenic value of the toxoid has been developed which promises to be helpful. In an earlier paper (*loc. cit.*), the writer reported that most adult white rabbits, as purchased in the open market by the National Institute of Health, when injected with one human skin test dose of toxin intradermally on the under surface of the pinna of the ear develop an area of inflammation (visible only by transmitted light) very similar in size to the erythematous area produced by a similar intradermal dose in susceptible persons. That this reaction is a toxic one is evident since it can be prevented by adding antitoxin to the toxin before injecting. Like-

wise it should be possible to prevent this reaction by stimulating immune body production in the rabbit through the injection of sufficient antigen. Eighteen rabbits, susceptible to one skin test dose of raw toxin, received from 15,000 to 25,000 skin test doses of raw toxin subcutaneously, a weighted mean of 20,000 STD per animal. At the end of two weeks thirteen of these animals gave no reaction to five skin test doses of test toxin when injected intradermally in the ear. As a control, ten susceptible rabbits each received subcutaneous injections of 0.2 cc. of plain broth. When retested two weeks later, all ten rabbits gave strong reactions to five skin test doses of test toxin. Twenty-one susceptible rabbits were given subcutaneous injections of 0.2 to 0.3 cc. of toxoid Td-16, a weighted mean of 0.25 cc. per animal, and when retested two weeks later, sixteen gave no ear reaction to five skin test doses of test toxin. In each of these tests the rabbits were also tested with a heated control (1 hour in streaming steam) of the same quantity as the test dose. A few animals reacted to the heated control and these were considered as negative when the reaction approximated in character that produced by the test toxin, an indication of pseudo-reaction. On the basis of these results, toxoid Td-16 would have the antigenic equivalent of at least 80,000 STD of raw toxin per cubic centimetre.

The raw concentrated toxin—table 1, toxin HL-32 W—contains 175,000 STD of toxin per cubic centimetre, which would indicate that the process of detoxification destroys some of the antigenic value.

The point has been raised by Okell⁸ and others, that any antigenic stimulation obtained from scarlet fever toxoid is probably provided by the residual skin reacting factor in the toxoid. Should this reasoning be correct, the degree of immunity obtained by the injection of a given volume of the toxoid should be no greater than that produced by the injection of a sufficient number of skin test doses of raw toxin to correspond to the skin test doses of residual skin-reacting factor in the toxoid. A total of 1.6 cc. of toxoid Td-16 has been used; or human immunization. With a residual of 500 STD per cubic centimetre in this toxoid, the 1.6 cc. would then represent the equivalent of 800 STD of raw toxin. Nine susceptible rabbits were each injected subcutaneously with 1.6 cc. of toxoid Td-16 and a similar number each received 800 STD of raw toxin. Two weeks later all were retested with one, two and one-half and five skin test doses, respectively, of test toxin and a heated control. Of the nine toxin-treated rabbits, four showed immunity to 1 STD of control toxin and none to 2.5 STD, whereas the nine toxoid-treated rabbits all showed immunity to 2.5 STD and five were negative to 5 STD.

ACTIVE IMMUNIZATION WITH SCARLET FEVER TOXOID

Approximately 1,700 persons having positive skin reactions to one human skin test dose of toxin have been treated with the detoxified toxin, prepared in the manner already described.

Throughout this study a skin reaction was considered positive if one skin test dose of standard toxin, when injected intradermally on the upper ventral

surface of the forearm, produced within 24 hours a reaction measuring 10 mm. in its greatest diameter irrespective of the intensity of the reaction.

In order to meet the requirements of practicability, and to meet the approval of physicians and parents, it was felt that the number of injections required should not exceed three and that the children treated should experience no incapacitating sequelae. (It scarcely need be added that disease preventive measures of this character are designed for the period of childhood and not for the adult.) At the same time, the object was to give each child no less antigen than is contained in the five immunizing doses of raw toxin as recommended by the Scarlet Fever Committee.

In the beginning of this study, antigenic value of the toxoid was calculated volume for volume the equivalent of raw toxin, though it was considered highly probable that some of the antigen would be destroyed by the detoxification process. However, with the development of a rabbit method of measuring antigenic value, it becomes possible to estimate the antigenic value of each batch of toxoid with at least fair accuracy.

A wide range of individual doses representing varying quantities of toxoid were tried during the course of this study in order to ascertain the maximum total volume of antigen tolerated as well as the minimum number of injections required. Sufficient toxoid to produce immunity in a high percentage of susceptible individuals could be given in two doses with an interval of one month between doses, as is demonstrated by groups A₃, C₁, C_{1A}, C₂, C_{2A}, C₃, E₂, E₃ and E₄ (see table 4). However, doses of the volume required did produce constitutional symptoms in a certain number of individuals. By distributing the necessary volume of toxoid into three doses it was possible to eliminate constitutional symptoms entirely in children and to reduce them to only a rare occurrence in adults. The three-dose method with three-week intervals was used with the other groups reported in table 4. The graduation of doses was not correct in each group so that a few individuals in some of the groups did develop constitutional symptoms, namely, fever, headache, and in a rare instance nausea without vomiting. From this experience it was possible to determine the tolerance range and subsequent clinical experience has shown that three doses of 0.1, 0.5 and 1.0 cc. of toxoid, respectively, diluted if neces-

TABLE 2. The reduction in toxicity of scarlet fever toxin through the action of formalin and storage at 37° C., as measured by the skin reacting factor.

Designation of toxin	Estimated potency of the raw toxin per cc.	Designation of the resulting toxoid	Period of storage at 37° C.	Quantity of formalin used	Estimated residual skin reacting factor per cc. after detoxification
1930	50,000 STD	Td 1	56 days	0.4%	1,000 STD
HL23WA	75,000 "	Td 11	56 "	0.3	500 STD
HL25WA	200,000 "	Td 12	69 "	0.4	500 STD
HL26WA	200,000 "	Td 13	48 "	0.4	1,000 STD
HL27WA	200,000 "	Td 14	82 "	0.45	1,500 STD
HL32W	175,000 "	Td 16	64 "	0.45	500 STD
HL32W	175,000 "	Td 20	88 "	0.45	500 STD
HL34W	175,000 "	Td 21	66 "	0.45	500 STD

sary to suitable volumes for injection, are tolerated without significant reaction provided the toxoid meets certain requirements. These minimum requirements are those of toxoid Td-16, table 2, which had been prepared from concentrated toxin HL-32W, table 1.

A detailed analysis of the individual doses of an average commercial toxin, offered for active immunization purposes, as compared with the three doses of toxoid Td-16, is shown in table 3.

Reactions Following Injections

The majority of children and all adults developed an area of erythema at the site of injection. This area varied from a few millimetres in diameter up to an area extending over half the skin area from shoulder to elbow on the injected side of the arm. The intensity usually reached its maximum in 36 to 48 hours. The colour was a dull, deep red as contrasted with the bright scarlet erythema occurring with scarlet fever itself. Induration occurred in a limited number of cases and when present was restricted to a smaller area than the erythema. All cases showing induration showed tenderness on palpation and those with more extensive induration had some localized pain.

Constitutional symptoms were essentially absent in all younger children and occurred rarely in older children. Of twenty-three children, age 4-17 years, held under careful observation, a temperature of 37.5°C. was exceeded eleven times for the three injections, the maximum observed temperature being 38.3°C. In a group of seventy children, including the above twenty-three, slight headaches were reported by five older children. No other systemic symptoms appeared. A third group of 219 children, 14 years of age or under, showed some local reaction in nearly each instance, with mild systemic symptoms reported in four of the older children. A fifth child, a boy of 10 years, became ill with dizziness, leg weakness and nausea within two hours of each

TABLE 3. A comparison of the five immunizing doses of raw scarlet fever streptococcus toxin as recommended by the Scarlet Fever Committee and the three doses of scarlet fever streptococcus toxoid suggested by the present study.

Raw scarlet fever toxin			Scarlet Fever Toxoid No. Td-16				
Dose	Skin test doses of toxin given per dose	Total mgm. of nitrogen given in each dose ¹	Dose	Skin test doses of toxin in each dose before detoxification	Estimated antigenic value of each dose after detoxification	Residual skin reacting factor present in each dose in terms of skin test doses	Total mgm. of nitrogen given in each dose
1	500	3.9	0.1 cc.	17,500	8,000	50	32.2
2	2,000	15.7					
3	8,000	62.8	0.5 cc.	87,500	40,000	250	161.1
4	25,000	196.2					
5	80,000	628.0	1.0 cc.	175,000	80,000	500	322.3
Totals.	115,500	906.6	1.6 cc.	280,000	128,000	800	515.6

¹These figures represent the mean of the 5 commercial toxins reported in Table 1, weighted by the potency of each. Total nitrogen in all instances is reported as milligrams per 100 cc. of toxin or toxoid.

of the first two injections. He felt entirely well again in a few hours and nothing further developed. The cause of this reaction is not clear, though it does not suggest a toxin reaction.

Twenty-four pupil nurses all developed local reactions of the character already described though somewhat more pronounced than with the children. No nurse showed a temperature above 37.7°C. and five nurses developed mild headaches. A group of thirty-six adults, 44 years or under, showed more pronounced local reactions, and ten developed systemic symptoms with two confined to bed with chills. There was no vomiting and none developed a rash.

With systemic symptoms essentially absent in the young and occurring only occasionally in the adult, and with the symptoms, when present, limited to fever, headache and chills, it was believed probable that they constituted reactions to something other than the toxin itself.

Pseudo-reactions

At the time of the original skin test, seventy-four persons of various ages received on the opposite arm an injection of one STD of control toxin which had previously been heated for one hour in streaming steam (approx. 99°C.). Likewise 653 persons who were originally skin positive were tested with a heated control at the time of the retest after immunization. The results in the two groups were as follows:

	Group I	Group II
Total persons tested.....	74	653
Negative to toxin and the heated control.....	55, or 74.3%	467, or 71.5%
Positive to toxin and negative to heated control.....	18, or 24.3%	145, or 22.2%
Positive to toxin and positive to heated control.....	1, or 1.4%	41, or 6.3%

In an earlier portion of this paper it was shown that a temperature of 99°C. for one hour destroyed only 88.9 per cent of the skin reacting factor, whereas the same degree of heat for four hours destroyed at least 99.78 per cent. Therefore, the frequency of pseudo-reactions in the above tabulation may be too high, due to a small amount of active skin reacting factor remaining in the heated control. It is evident that with this particular control toxin, the test for pseudo-reactions should be made with the same toxin after exposing it to streaming steam for four hours. However, if a test toxin of high titre is used (the National Institute of Health standard toxin contains 45,000 STD per cubic centimetre), pseudo-reactions become of such infrequent occurrence in children that for routine purposes the test may be omitted. Even in the presence of a pseudo-reaction the symptoms developing in the treated individual are sufficiently mild and transitory not to be significant.

First Retest after Immunization

An attempt was made to retest each treated person one month after the injection of the last immunizing dose. Of 1,700 persons so treated, 1,168 were available for this retest and of these 972, or 83.2 per cent, were Dick

negative. Table 4 is presented to show the age range of the various groups treated, the lot number of the toxoid used, and the results of the retest in the various groups.

TABLE 4. The number of Dick positive persons given injections of scarlet fever toxoid and the character of the skin reaction upon retest with one human skin test dose of toxin, one month after the last immunizing dose.

Designation of group	Age range in years (both inclusive)	Lot number of toxoid used	Retest one month after last immunizing dose		
			Number retested	Number negative	Per cent negative
A ₁	6-13	Td 1	21	20	95.2
A ₂	3-14	Td 11	22	19	86.3
A ₃	4-14	Td 12	22	21	95.5
B ₁	18-22	Td 1	17	12	70.6
B ₂	18-22	Td 1	10	9	90.0
B ₃	18-22	Td 13	13	10	77.0
B ₄	18-22	Td 13	10	9	90.0
B ₅	15-18	Td 11	9	8	89.0
C ₁	5-16	Td 12	47	36	76.6
C _{1A}	17-53	Td 12	52	41	80.8
C ₂	2-16	Td 12	145	109	75.1
C _{2A}	17-46	Td 12	133	106	79.6
C ₃	6-17	Td 12	24	16	66.5
D ₁	2-16	Td 12	147	124	84.4
D ₂	1-16	Td 16	85	71	83.5
E ₁	2-19	Td 12	116	94	81.0
E ₂	5-16	Td 13	10	10	100.0
E ₃	17-55	Td 13	91	87	95.6
E ₄	18-52	Td 13	70	63	90.0
F ₁	2-21	Td 11	31	27	87.1
G	5-15	Td 1	93	80	86.0
Totals.....	2-55		1,168	972	83.2

The Dick positive inmates of three institutions, not included in table 4, which care for tuberculous children, were treated with three doses of toxoid Td-16. On retest the skin reactions were as follows:

Institution	Elapsed time since last injection	Number present for retest	Per cent negative on retest
C ₄	4 weeks	73	80.9
C ₅	4 weeks	89	82.0
C ₆	10 weeks	97	51.5

Institutions C₄ and C₅ were again retested approximately ten weeks after the last injection so as to give information comparable to Institution C₆ when the per cent negative was 70.1 and 59.6, respectively. The results are considerably lower than the retests reported for well children in table 5. The children in these institutions were in various stages of tubercular infection and in addition Institution C₆ went through epidemics of mumps and "grippe" during the immunization period. It is not known what influence such intercurrent diseases may have had on the production of scarlet fever immunity. It may

also be that the secondary infections invariably present in pulmonary tuberculosis have caused an excessively high percentage of pseudo-reactions. Unfortunately, no heated control test was made.

TABLE 5. Presented to show the durability of the skin negative phase following the injection of scarlet fever toxoid, in so far as this study has progressed. This table contains data on all persons included in table 4 who were present for the second retests except groups C₁, C_{1A}, C₂ and C_{2A} which are separately reported.

Designa- tion of group	Number immunized and Dick tested on two occasions	First Retest			Second Retest		
		Elapsed time before first retest	Persons negative		Elapsed time before second retest	Persons negative	
			Number	Per cent		Number	Per cent
A ₁	14	1 month	13	92.8	29 months	14	100.0
A ₂	19	"	16	84.2	13 "	17	89.5
A ₃	16	"	15	93.7	12 "	15	93.7
B ₁	11	"	9	81.8	22 "	9	81.8
B ₂	5	"	5	100.0	18 "	5	100.0
B ₃	13	"	11	84.6	10 "	10	76.9
B ₄	9	"	8	89.0	7 "	8	89.0
C ₃	15	"	8	53.4	9 "	12	80.0
D ₁	111	"	96	86.5	10 "	85	76.6
E ₁	114	"	96	84.1	7 "	102	89.5
E ₂	9	"	9	100.0	4 "	8	89.0
E ₃	82	"	79	96.4	4 "	75	91.5
E ₄	53	"	46	86.8	4 "	47	88.7
F ₁	23	"	19	82.6	9 "	22	95.6
	494		430	87.3	8 months	429	87.0

Influence of Age on Immunity Production

Of the 1,168 persons reported in table 4, it was possible to study the relations between the age of the individual treated and immunity production in 848 persons. As the following tabulation indicates, age does not appear to be a factor.

Age	Number retested	Per cent negative	Age	Number retested	Per cent negative
1	2	...	10	61	86.9
2	14	78.6	11	57	82.5
3	29	72.4	12	55	83.7
4	37	78.4	13	38	79.0
5	38	79.0	14	45	80.0
6	36	86.1	15	25	76.0
7	47	74.4	16	28	92.9
8	86	84.9	16 and over	198	78.2
9	52	88.5		848	81.3

Second Retest after Immunization

A second retest on as many of those persons reported in table 4 as were available was made shortly before preparing this manuscript, at which time 773 persons were present who had also received the first retest. Of this

number, 494 (table 5) had received no subsequent treatment, and of these, 429, or 87.0 per cent, were negative on the second retest as compared with 430, or 87.3 per cent, negative on the first retest. The mean weighted elapsed time in this group was eight months. The remaining 321 persons who were present on the second retest, groups C₁, C_{1A}, C₂ and C_{2A}, respectively, were treated somewhat differently in that those who were positive on the first retest were given additional injections of toxoid. Their second retests gave the following results:

Of 118 persons, 16 years of age or less, who had received two immunizing doses and were negative on the first retest, 105, or 89 per cent, were negative on a second retest 9½ months later.

Of 128 persons, over 16 years of age, who had received two immunizing doses and were negative on the first retest, 111, or 85.9 per cent, were negative on a second retest 9½ months later.

Of 75 persons of various ages, who had received two immunizing doses, all were positive on the first retest. An additional dose was given to 55 of these and after a lapse of 8½ months 35, or 63.6 per cent, had become negative. Three additional doses were given to the remaining 20 and after a lapse of 6 months 17, or 85 per cent, had become negative.

An analysis of the record on each person reported in Table 5 shows that there were few changes in the individual skin reactions from one test to the other. Thus, of the 494 persons tested on the two occasions,

385, of 78.0 per cent, were negative on both tests;

45, or 9.1 per cent, were negative on the first test and positive on the second;

20, or 4.0 per cent, were positive on the first test and positive on the second;

44, or 8.9 per cent, were positive on the first test and negative on the second.

If the size and intensity of the skin reaction can be taken as a criterion, those persons whose skin reactions were still positive at the time of the second retest seem to have built up some immunity. The mean original reaction of ninety-three such individuals measured 21.3×27.7 mm. as compared with a mean measurement of 12.3×15.9 mm. for the same persons on the second retest when tested with some of the same lot of control toxin.

The reactions had been reduced in size in all instances save three, and with these the mean had increased from 8x12 mm. to 14x17 mm. The intensity of the retest reactions was either diminished or the same in each of the ninety-three persons.

How does the percentage of susceptibles who are rendered Dick negative following the injection of toxoid compare with the results obtained with the injection of raw toxin? Since the attempt was made to approximate in the toxoid dose the same amount of antigen as is contained in the dose of raw toxin recommended by the Scarlet Fever Committee, it is to be expected that the percentage of immune resulting from the two treatments would be about the same. The results following treatment with toxoid have been presented in tables 4 and 5. There are presented in table 6, results reported by different workers with raw toxin immunization. Of the groups reported in table 6, only the first three received five injections containing the quantities of toxin which are now recommended by the Scarlet Fever Committee, namely, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses, respectively, with weekly intervals. Literature contains very few reports of this character which are in sufficient detail for comparative purposes.

Prevention of Scarlet Fever

The purpose of the clinical phase of this study has been to observe the tolerance of the toxoid injections and the subsequent effect on the skin reaction.

TABLE 6. The influence of injections of raw scarlet fever streptococcus toxin on the skin reactions of persons known to be susceptible. Both the original skin tests and the retests were made with one skin test dose of toxin.

Reported by	Number of persons retested	Total dose of raw toxin given	Interval between last dose and retest	Per cent negative to 1 STD of toxin
Anderson 1, 5.....	60	115,500	1 year	83
Rhoads 2, 5.....	298	115,500	2 weeks	81
Smythe and Nesbit 3, 5.....	197	115,500	2 weeks	85
Smythe and Nesbit 3.....	3,255	85,500	2 weeks	66
Dyer 1.....	34	62,000	3½ years	91
Dyer 1, 6.....	122	42,000	13 days	96
Dyer 1, 6.....	107	42,000	10 months	64
Kiefer 4.....	114	35,500	1-2 years	61
Kiefer 4.....	41	34,000	2 years	66
Kiefer 4, 7.....	577	5,000+	3 years	77
Kiefer 4.....	799	5,000	21 days	39

1. Unpublished data.

2. *J. A. M. A.*, 97: 153-156 (July 18), 1931.

3. *J. Prevent. Med.*, 2: 243-250 (May), 1928.

4. *J.A.M.A.*, 91: 1885-1888 (December 15), 1928.

5. The total dose injected in these groups represents the amount of toxin now recommended by the Scarlet Fever Committee.

6. The same group tested on two different occasions.

7. All these persons received 5,000 STD plus such additional quantities, in 5,000 STD doses, as were needed to render the skin reaction negative within a few weeks (the exact amount is not stated).

However, in a very limited way there has been an opportunity to observe its protective value in human subjects. Scarlet fever had appeared each season in two of the institutions used. Following the treatment of those Dick positive, one institution has remained free from scarlet fever while the other has had no cases among those immunized but only in more recent admissions of unknown susceptibility. Two other institutions have had cases appear among untreated persons who were known to be skin positive but not in those immunized. A fifth institution experienced an outbreak of scarlet fever among recent admissions who had been neither tested nor treated. To date no cases have developed in the treated population or in persons known to be Dick negative. These experiences are too limited and indefinite to provide evidence for conclusive deductions but are suggestive. There is need for an immunization test on a community-wide basis with the retention of a satisfactory control group of known positive children living under identical conditions and of the same age range.

SUMMARY

A method has been presented for the concentration of the toxin which is elaborated by the hemolytic streptococcus of scarlet fever origin by which the toxin content is increased approximately four-fold without causing an increase in the total nitrogen content of the preparation above that now present in commercial unconcentrated toxins. This concentrated toxin may be detoxified by the action of formalin and storage at 37° C., in approximately 60 days so that there remains less than one-half of one per cent of the skin reacting factor. This residual appears to be irreducible through continued storage. Its character is not fully understood, though it appears to be neutralizable by antitoxin.

Single injections into susceptible white rabbits indicate that this detoxified product

possesses antigenic properties, though the detoxification process apparently does destroy a portion of the antigen.

Tests on susceptible persons indicate that toxoid, possessing the characteristics of toxoid Td-16 which is described in the text, may be given in a three-dose method to children under 15 years of age without subsequent reactions except local erythema in a majority of children, accompanied by induration in a few and tenderness in a still smaller number and mild systemic symptoms (slight fever, headache) in only an occasional individual. Of 1,168 persons retested with one STD of control toxin one month after the last injection, 972, or 83.2 per cent were Dick negative. Of 494 persons retested again, an average of eight months after the last dose, 87.0 per cent were negative as compared with 87.3 per cent on the first retest.

In conclusion it should be emphasized that the results reported in this study were obtained through the use of a single strain of hemolytic streptococcus which had been cultured in the manner described. It is not known whether similar results could have been obtained through the use of other strains and other methods.

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When a Province Tackles Tuberculosis*

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TUBERCULOSIS is an age-old disease with ramifications throughout the whole social system, and a proneness to infect house groups. The strategy of our attack must be based on a fact so fundamental that every school-boy should know it—the fact that as life comes only from life, so tuberculosis comes only from tuberculosis. This infectiousness of the disease is the try-square by which all our effort should be measured. Each diseased person is a potential scatterer, usually a daily, hourly scatterer, but sometimes only a rare occasional scatterer, of infection. Our first big job is to find diseased people and make them safe by treatment, by segregation, by education, safe for themselves, safe for their families, safe for their communities, safe anywhere and at all times. Our next job is to follow clues wherever the evil seeds have scattered; that is, to examine repeatedly all contacts and suspects. Ultimately we should aim at a survey of the whole community. At some future day we may have universal, adequate, periodical, routine medical examinations, and these should come nearer to conquering tuberculosis than any other measure whatsoever. But in the meantime the most we can do, and the least we must do, is to follow up all clues of known disease.

And though tuberculosis is an infectious disease like small-pox or diphtheria or scarlet fever, it is also unlike small-pox or diphtheria or scarlet fever. Infections that incubate in a week or two, and are over for good or ill in a month or two, call for measures that would be entirely out of place for an infection that may take forty years to develop into evident disease. One needs an efficient public health organisation with stern backing of the law: the other a wide, deep, detailed knowledge of all the ways of the protean disease, a great deal of understanding of those who suffer from it, and sympathy for them, and the co-operation and help of every private practitioner.

If the anti-tuberculosis effort of a province is merely a patchwork of bits of effort here and there, it is not good enough to deal with such a situation. The whole field should be mapped out, the whole need envisioned. Each agency should have its own bit of work, its own parish, and in that parish should go out into the highways and hedges to find need and give help. In Saskatchewan the whole anti-tuberculosis work of the province is under one very efficient organisation.

*Presented by F. W. Jackson, M.D., D.P.H., at the 21st annual meeting of the Canadian Public Health Association, Toronto, May, 1932. In some particulars data of 1932 and 1933 are included for publication.

Minnesota for years, besides its state and county associations, has had a loose but useful federation of all the sanatoria. Manitoba has not Saskatchewan's unity of control, but has a general Sanatorium Board for the province. This board directly controls one sanatorium, one permanent clinic centre, and the travelling clinics. Two other centres, a sanatorium and a tuberculosis hospital, are not under the control of the board but are loosely affiliated. They are represented on the general Sanatorium Board, and co-operate in the general plan. The Provincial Departments of Health and Municipalities, the Union of Municipalities and the provincial Medical Association are all represented on the general Sanatorium Board. An advisory board, a board of co-operation of all anti-tuberculosis agencies, should be practicable even in a large and complex province or state. Within the framework of a general plan every unit of energy can be free to work its own miracles.

THE NEED OF BEDS

In any general scheme sanatorium or hospital beds are still a primary need. Community safety demands the treatment of tuberculous people as early, as late and as long as treatment is necessary, the segregation in institutions, or the effective control at home of spreaders while they are spreaders, and as soon and as long as they are spreaders. The standard used to be one tuberculosis bed for each annual tuberculosis death; now we know that we need two tuberculosis beds for each annual death. Of course where the onus is on the individual and not on the state, and the individual must pay for his treatment or not get it, even one bed for each annual death will likely not be filled. No province in Canada had its sanatorium doors more widely open than Saskatchewan, and yet when free treatment for all tuberculous people, whether able to pay or not, came in, the patients under treatment increased by 25 per cent in a month or two. At any rate, an essential in any effective anti-tuberculosis programme is beds, beds waiting for the people, and not people waiting wearily month after month for beds; beds for treatment, for observation, for segregation and isolation, even beds to die in, so that family and friends may not suffer from the last fatal scatterings of infection. What is the use of finding sick and infective people if we can just wish them well and leave them as we find them?

On the other hand, there is a limit to the amount of tuberculosis hospitalisation the community can pay for. The disease is often life-long, yet life-long treatment is out of the question. Even beds for all infective people are out of the question. And institutional care from year to year for all who are invalids or wrecks because of tuberculosis, is out of the question. And chronic, more or less latent tuberculosis complicated by unemployment has to be denied the attractive sheltered

life of the sanatorium. Whom to treat, and for how long, and to what stage of improvement, and who, though tuberculous, should be refused treatment, are questions that have to be considered and settled many times each day wherever tuberculosis is dealt with.

TRAVELLING CLINICS

With ten millions of people scattered along nearly four thousand miles of base line, and tapering toward the Arctic Circle, Canada needs mobile clinics. No two provinces need follow exactly the same plan, but each should have its own individuality, indigenous to its own soil. But there are general principles common to such clinics wherever they may be. They should integrate closely with all other anti-tuberculosis agencies, with sanatoria, with public health departments and the work of the public health nurses. Especially should they be in close touch with physicians. The best of all health officers is the disease-prevention-minded family doctor. The tuberculosis clinic is the consultant of the family doctor. It should get its cases from or through him, should work with him, report to him, keep in touch with him.

Travelling clinics must set high standards, for they work constantly along the diagnostic borderline. The best facilities and the best judgments are none too good for decisions about contacts who are usually not yet ill, and with no signs nor symptoms. Along this borderline the X-ray film, and a good one, is an absolute essential. Without it clinic physicians would be often but blind leaders of the blind.

Yet clinics, and, of course, sanatoria and hospitals also, must do the greatest good to the greatest number at the least cost. When John Gilpin's wife unfolded her plans, he "was pleased to find, that though on pleasure she was bent, she had a frugal mind." Travelling clinic work, or any anti-tuberculosis work, or any welfare work in these days should cost not one cent more than it must cost. Bits of elaborateness that may be very desirable must sometimes be cut out, and work reduced to essentials. The essential fact is the exact diagnosis. Single films will usually settle the question; stereo or oblique films will be needed rarely. The man who makes two blades of grass grow where one grew before is no better citizen in these days than the man who makes two useful examinations with the same outlay with which one was made before.

When clinics have to create new separate bases and new special staffs they must be more costly than clinics using existing bases and staffs. An existing sanatorium, for instance, with its general organisation and staff should be able to do travelling clinic work with maximum efficiency at minimum cost. Nothing does a sanatorium staff more good than such missionary work. They are better sanatorium men if they have clinic work also to do, and better clinic men because their main work is the orderly and organized work of the sanatorium. Everything

is for such a plan. In Manitoba, travelling clinics are simply a part of the year's work of the Manitoba Sanatorium, assisted by the Public Health Nursing Service. In the past few years the cost has been borne by the sale of Christmas seals. The "outfit" has grown until now it has a special van for personnel and equipment, and even a portable generator, so that clinics can be held quite independent of hydro or local electric currents.

In the travelling clinics a very important partner has been the Public Health Nursing Service. For a population, outside Winnipeg, of about 400,000, Manitoba had, until recent staff reductions in the interest of economy, 54 public health nurses. Before a clinic, a public health nurse, co-operating with the local doctors, and with lists of known foci of infection or suspicion, visits each family and ensures attendance. After the clinic, and during the whole interval between clinics, the nurses keep in touch with patients and doctors. And all the year round reports come and go and useful information about scattered patients is made available to all concerned.

The whole cost of these clinics, apart from the services of public health nurses, was \$2.27 per person examined in 1931, and \$1.72 in 1932. Practically all examined had X-ray film or films. The proportions of the non-urban population of Manitoba examined by travelling clinics only, in the past three years have been one in 140, one in 170, and (1932) one in 78. For comparison, the proportion of the population of Greater New York examined in the Associated Charities Clinics in 1931 was one in 130. There is no doubt that travelling clinics can cover their parish with an efficiency equal to city clinics, and even at equal cost.

While local statistics should always be used sparingly in a general discussion, a few facts beyond those given above may be made palatable. From a small beginning seven years ago with two clinics and 165 examinations, the work has grown until in 1932 alone, 5,102 examinations were made in 47 clinics. Altogether nearly 16,000 examinations have been made in 127 clinics at 58 different centres. Of those examined, 56 per cent were known contacts, and 48 per cent children. Nearly two thousand of the sixteen thousand examined had tuberculosis known or previously unknown. In 1932 alone *269 new discoveries of tuberculosis* were made, and *1,078 new discoveries* in the whole series, nearly seven per cent of all examined. Besides tuberculosis, clinics called attention to other abnormal and disease conditions to the number of nearly 15,000, of kinds so numerous that a half a page would scarcely even name them all.

GENERAL STANDARDS

Standards are constantly changing. No one would think of building a sanatorium on the "shack" plan to-day, though this was the

approved plan not much more than twenty years ago. What standards are applicable for to-day to a general provincial tuberculosis programme? Dr. Willard B. Soper of Yale University has worked out such a series of community measuring sticks.

The basis of most measurements is the number of tuberculosis deaths per year. As has been already stated, the number of tuberculosis beds a community needs is now—and rightly—set at two per annual death. Another need is tuberculosis not only a reportable disease, but a disease reported. The United States' full score for the present is two cases reported per annual death, but New Haven has nearly four cases reported per annual death. So standards go up. Try this measuring stick on your province. For each annual death in Framingham, a thorough survey revealed eighteen definitely diagnosable cases for every annual death—nine active, and nine arrested. And by the smallest estimate there are three contacts to each active case. To the nine active cases per annual death add the death itself, making ten points of contact, and multiply by three. That shows thirty contacts per annual death. Try this measuring stick also, and put your trust more and more in surveys and clinics and travelling clinics.

"How long should you follow up this child who has minimal healed disease?" an experienced tuberculosis worker was asked. "Until he dies of old age," was the reply. And really, once tuberculous always tuberculous. Children with disease of latent type, the standards above quoted say, should be followed until twenty-five. The Canadian improvement upon that rule should be, "And not let entirely out of observation even after that." Other standards given by Dr. Soper are, a full time clinician for diagnosis for every 100,000 population, reports upon "contacts" half-yearly, eight nurse visits a year to a diagnosed patient at his home, the following of all diagnosed patients until death or removal, 5,000 nurse visits and 25,000 to 50,000 days' treatment for every hundred annual tuberculosis deaths, and 2,500 visits per nurse per year in an urban community. The public health aspects of tuberculosis are being more and more urged. Bacilli positive cases are given preference for admission to hospital or sanatorium. A manageable city survey might be, tuberculin tests of all children and X-ray films of all reactors. Such a survey would yield in an average American or Canadian city possibly 50 per 100,000 examined who have active pulmonary tuberculosis, 100 per 100,000 with latent apical disease, 100 per 100,000 with latent disease of lung parenchyma, and 10,000 with evidence of inactive healed tuberculosis in tracheo-bronchial glands.

To get a good marking a community should so round up its cases that 25 per cent of first diagnoses will be at early stage of disease. Notification should be compulsory. It is urged also that there should be laws about the cleansing of infected premises, laws to control the

recalcitrant case, a law giving authority to separate diseased adults from children, and laws against careless spitting. These laws are quite logical, but let any community proceed with such laws most carefully. Laws, however logical, must never be allowed to drive diseased people or suspects "under-ground." If the show of force in one forced-in case raises a hub-bub that keeps a hundred cases out, what does it profit? The Canadian instinct here is for a minimum of laws.

GENERAL PRINCIPLES

There are a few other general principles for a province that tackles tuberculosis. Late stages of disease should be treated as well as early, and early as well as late. What was hopeless ten years ago may not be hopeless now. To care for a dying man is a measure of prevention. But to have had that man for treatment years ago would have been an all-round personal and community gain.

The whole field must be covered with treatment, with diagnosis, with following of clues, with preventive measures, with education. Every tuberculosis agency should have its own field of work, be it city, county, province or state, and all within that area that relates to anti-tuberculosis efforts should be framed into a common plan. It is a primary and principal duty of a sanatorium to do systematic missionary work outside its walls and throughout its territory. When one man in a province is tuberculous, that province is tuberculous. Treatment of the sick man may make the stronger appeal, but treatment of the infected state is the more important measure. Cure is good, but prevention is better. There are two separate interests, though they are closely allied, the interest of the man diseased and the interest of the state, and the interest of the state is paramount.

Early disease does not declare or report itself, or come automatically for treatment, but must be hunted for. Much the same is true of moderately advanced or advanced disease. It also must be hunted for. Tuberculosis left to find itself usually staggers in hopeless, after spreading seeds of disease broadcast throughout family and community. If people are to be made safe for themselves and the community, at the right time and in the right way, they must be hunted for.

The care of the tuberculous should impose as little financial burden as possible on the patients themselves. With a long-drawn out disease payment is almost always a hardship, or in time becomes a hardship. The need of paying almost always tends to postpone or limit the time of treatment, and often prevents treatment altogether. The burden of treatment of the indigent should be carried by the community in some form, and there is no good reason why the treatment of ordinary good citizens should not be at least in part carried in the same way. All diagnosis, treatment, segregation and observation of a tuberculous person is diagnosis, treatment, segregation and observation for the benefit of the community.

In almost all provinces there are people especially susceptible to tuberculosis. In the United States the negro tuberculosis death rate is four times that of the white race, and the rate for Mexicans in United States cities is terribly high. In Canada the Indian tuberculosis death rate is ten times the white; in Manitoba, twelve times the provincial average. Throughout the whole Dominion Indian groups create hotbed centres for the cultivation and spread of disease. No line can be drawn that will keep us safe from this source of infection. Racial infiltration alone spreads the disease widely. The only way of making the ordinary citizen safe from Indian tuberculosis is to do something systematically for Indian tuberculosis.

WHAT A PROVINCE SHOULD AIM AT

Even in the white population the incidence of tuberculosis is unequal, with such variants as country of birth, racial origin, intelligence, economic status, and the general disarrangements of life due to emigration.

Present ideals for a province that would really tackle tuberculosis might very well be: every sick person found as early as possible and given the best chance for recovery; every spreader segregated, or instructed and watched; every social focus of tuberculosis investigated; every contact or suspect examined, and re-examined; every physician, medical student, nurse, and indeed every responsible citizen made interested in tuberculosis problems, and better instructed about them; co-operation of all agencies, under a general plan, to these ends; the utmost economy, the most that can be had for the money, maximal results with minimal cost; and, not least important nor least difficult, a way for distributing the burden of cost on the community most equitably, and carrying it most easily.

Nutrition in Relief Work

(May, 1933)

Page 210, line 20: for "lower" read "higher".

Page 220, line 22: omit "not".

Page 221, line 19: "*or* unless local prices are unusually low."

The Registration of Non-Resident Births and Deaths

I.—From the Urban Standpoint*

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IT is becoming increasingly apparent to those responsible for the interpretation of municipal vital statistics that mortality rates for a municipality must be calculated with greater precision than has been possible heretofore. The present system of calculating from the number of births and deaths registered at the place of occurrence may present a distorted picture of prevailing health conditions in a community.

The difficulty arises from the fact that statistics for municipalities include births and deaths occurring among non-residents and exclude those of residents occurring elsewhere than at their usual place of abode. Thus a city possessing recognized hospital facilities for medical and surgical care will suffer in the comparison of its mortality rates with those of other cities less fortunately placed in this respect. The same argument applies to those communities in which mental hospitals, sanatoria and other institutions are located adjacent to large municipalities.

We may take a concrete and relatively uncomplicated example in the case of acute communicable diseases. Here a large city may have isolation hospital facilities which are used by patients from surrounding districts. Fatalities occurring among these patients will increase the city's crude death rates. On the other hand, an isolation hospital may be located outside the municipal boundaries, in which case the city's crude rate for this class of disease may appear minimal.

Two recent studies, covering the year 1930 mortality rates from diphtheria and typhoid fever respectively, in ninety-three cities of the United States, illustrate this existing fallacy. They also indicate how readily an erroneous conclusion may be reached that a particular city is negligent in its application of the well recognized methods of control in the case of these two diseases.

In table I of the report on diphtheria mortality in fourteen New England cities, Providence ranks fourth highest with a rate of 7.9. This rate is based upon the twenty deaths which occurred in this city during 1930. We find that fifteen of the deaths occurred among non-residents brought to the city for treatment. How could one estimate from such a crude rate the efficiency of methods which may have been instituted in that city to reduce mortality from this preventable disease? In two other cities but a single death from diphtheria occurred, and in each case the patient was a non-resident. In yet another city, three deaths occurred, of which all were non-residents. Thirty per cent or more of the diphtheria deaths reported for Camden, Cincinnati, Jacksonville, Knoxville, Tampa and Trenton occurred among non-residents of these cities. On the other hand, the isolation hospital of Grand Rapids is located outside of the city, and a rate of 0.6 is shown. It is stated that the actual rate would be nearer 3.0.

The second study, dealing with typhoid fever, also emphasizes the fact that more attention must be given in future investigations to the factor of residence in calculated rates of mortality. This study of typhoid fever mortality, as the one of diphtheria outlined above, is based upon the number of deaths registered at place of occurrence, and the figures were obtained from the respective health departments of the cities therein enumerated. It is pointed out that non-

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resident deaths offer an important problem in a number of cities. In four of these cities, only a single death occurred from typhoid fever, and in each case the death was that of a non-resident. In twenty-seven other cities, non-resident deaths amounted to one-third or more of the total deaths reported from this disease. Both these studies bring into question the validity of conclusions drawn from rates uncorrected for residence.

Non-Resident Births and Deaths in Toronto

As one might expect, similar fallacies exist at the present time in many of the published mortality rates for municipalities in Canada. The city of Toronto comprises one of the largest hospital centres in Canada. Of the 7,017 deaths which occurred in this city from all causes during 1930, 1,060 or 15.1 per cent were those occurring among non-residents. Non-resident births were in excess of 1,600, or over 12 per cent of the total number.

On account of Toronto's excellent facilities for the isolation and treatment of acute communicable diseases, one-quarter of all the deaths occurring in 1930 from these causes were those of non-residents. During the same year, the percentage among causes in early infancy was 17.5; gastro-intestinal diseases, 21.4; and accidental deaths, 18.6. The percentage for tuberculosis, cancer, diabetes and pneumonia ranged from 12.1 to 16.7 per cent. Toronto's hospital facilities attract many maternity cases from outside of the city. The resulting fatalities among these mothers constituted 30 per cent, or 27 of the 90 deaths which occurred in the city from puerperal causes in 1930.

These facts show the significance of the number of non-resident births and deaths occurring in our own municipality. On the other hand, a general hospital is situated immediately beyond the northern limits of the eastern section of the city. During 1930, 455 or 74 per cent of the total births, and 119 or 66 per cent of the total deaths which took place in this hospital occurred among residents of the city of Toronto. These events, of course, are not registered at the place of residence. In outside sanatoria, 115 Toronto residents died from tuberculosis. This is merely the number of which we have knowledge, due to the fact that the city contributes to the maintenance of its indigent residents in outside public sanatoria. At the present time, for practical purposes, Toronto depends upon these inadequate sources of information in order to partially correct its rates.

Rates for *acute communicable diseases* may be corrected on the assumption that the number of resident deaths occurring elsewhere would be but a negligible quantity. Upon this basis, the whooping cough death rate is reduced from 1.93 to .96; infantile paralysis from 4.34 to 3.22; typhoid fever from .64 to .48. The rates are the same for measles, while that for diphtheria is reduced from 11.1 to 8.7. Such adjustments appear necessary in calculating the fatality rates (deaths per 100 cases) if we are to show the virulence of these diseases when epidemic, or if we desire to measure the effectiveness of an immunization campaign.

While Toronto's *maternal death rate* is shown as 6.6, partial corrections, on the above basis, show the resident rate to be nearer 5.2. Considerable attention has been recently focused upon maternal mortality, and the information thus provided is of much significance to the health officer and those engaged in maternal welfare work. By similar corrections, a material reduction

is evidenced in Toronto's infant death rate. On the other hand, the rate for tuberculosis, based upon deaths occurring in the city, which is 42.3, becomes 53.7 when corrected for the 115 deaths in outside sanatoria. At best, these corrections can only be termed partial, but for practical purposes they serve to better advantage than crude rates in indicating sanitary conditions existing in a municipality.

On general principles, it has been the custom in Toronto (as in practically all larger cities) to publish statistics for the city based upon events registered at the place of occurrence. In other cities where the number of births and deaths is much smaller than that for Toronto and the distribution of resident decedents not nearly so extensive, it has been possible to arrive at rates virtually corrected for all residents. In the case of Toronto, however, the area of necessary investigation is too great to secure a similar degree of accuracy without considerable outside assistance. Nevertheless, it is our intention this year, with the help of additional personnel and the permission of our provincial registrar, to sort out all registrations of Toronto residents, with a view to publishing statistics for this city, corrected by residence, within the limits of the province of Ontario at least. This appears to be as far as any municipality can proceed unaided, towards correction of its own statistics under present conditions.

The whole problem of non-residents is most confusing and much time and labour is consumed in their classification and tabulation. It is suggested that the problem of re-allocation by residence could be more adequately undertaken by the provincial or Dominion authorities. Municipalities with organized statistical departments could co-operate effectively in this work, and would be glad to do so in order to obtain weekly and monthly figures corrected for residents only. Such facilities would, moreover, be of very great assistance in the compilation of an annual report to the medical officer of the municipality concerned.

The system of re-allocation has been carried out in England since the beginning of 1911, with the Registrar General's office acting as a clearing house. In many of the American states re-allocation is made by the division registrar, who is also the local medical officer of health.

*II.—From the Provincial Standpoint**

PAUL PARROT, M.D.

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NON-RESIDENT DEATHS

Residents of the United States

ONLY in the past two or three years has an attempt been made in the United States to solve the supposed problem arising from non-resident deaths. In 1929 an agreement was made between my office and the registrar of New York State to interchange copies of such deaths. Such an

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interchange was to be made with all the other states and I suppose that the registrars of the other Canadian provinces have had a similar understanding. Since then I have forwarded to the states concerned copies of our death certificates concerning American citizens dying within our territory.

During the past two years I have thus obtained some interesting figures concerning the total number of Americans who died in the province of Quebec and the number of Quebec people who died in the United States. Table I shows the total number of deaths of American citizens which were registered in the province during 1930, with the month of occurrence and the place of residence. Earlier figures pertaining to "international" non-residents are not, I believe, available.

TABLE I
AMERICAN CITIZENS WHO DIED IN QUEBEC DURING 1930

State	Month of death											
	J.	F.	M.	A.	M.	J.	J.	A.	S.	O.	N.	D.
Florida.....							2					
Maine.....	2				1			1	1			
Maryland.....							1	1				
Massachusetts.....						1	1			1		
Michigan.....						1					1	
New Hampshire.....									3			
New Jersey.....								1				
New Mexico.....								1				
New York.....					1	2	1	6	1	2		2
Ohio.....			1						2			
Pennsylvania.....						1					2	
Rhode Island.....					1							
Vermont.....							1			1	1	2
Others.....				1	1		3	2	2		2	1
Totals.....	2	1	1	0	4	3	10	12	8	4	6	5

From this table we see that the largest number of American deaths in the province occur in the summer. Of these 56 deaths, 18 (32 per cent) were the result of automobile accidents, several of which were responsible for more than one death.

The following table, II, gives the returns from American states in which citizens of Quebec died during 1930. For these 27 citizens I received copies of death certificates from the state registrars. The deaths, however, were not included in the total number of deaths for the province.

TABLE II
QUEBEC CITIZENS WHO DIED IN THE UNITED STATES IN 1930

Connecticut.....	3	New York.....	7
Florida.....	2	Rhode Island.....	1
Maine.....	3	Vermont.....	3
New Hampshire.....	4	Others.....	4
Total: 27			

From these tables one may conclude that there exists a fairly complete interchange between the United States and the province of Quebec, an interchange carried on as a means of ascertaining the importance of the question

of international non-residence. This interchange does not entail extra work at present, as the number of extra-territorial non-resident deaths is small.

Residents of Canadian Provinces

In dealing with the question of non-residence among our own provinces, the problem is somewhat different. Each month, transcripts of our provincial certificates, including those of provincial non-residents, are forwarded to the Dominion Bureau of Statistics. According to the present agreement, deaths must be computed according to the place of death. To my knowledge no attempt, however, has yet been made to interchange among the provincial registrars the certificates of all non-resident deaths. From my records of returns to the Bureau, I am able to give only the total number of deaths of Canadians who were not domiciled in our province but who died within our territory. These data are given in Table III.

TABLE III
CANADIANS FROM OTHER PROVINCES DYING IN QUEBEC IN 1930

Province of residence	Month of death											
	J.	F.	M.	A.	M.	J.	J.	A.	S.	O.	N.	D.
British Columbia.....	1		1							1		
Alberta.....	1				1				1			1
Saskatchewan.....	1		4	1	1			2		1		
Manitoba.....		1	3			1				3	1	
Ontario.....	11	9	16	6	9	7	4	9	7	10	5	6
New Brunswick.....	5	3		3	2	1			3	1	1	1
Nova Scotia.....	2		1	4	1		1	2	2			1
Prince Edward Island.....		1							1	1		
Totals (162).....	20	14	25	14	14	10	5	13	15	16	8	8

As shown by this table, we know how many Canadians not domiciled in Quebec have died in the province, but we do not know how many residents of Quebec died in other provinces. However, I am able to supply some figures as it happens that when a resident of our province dies elsewhere and burial takes place in Quebec, our Collector, officiating at the burial, forwards to the office a death certificate with the transportation permit. As a result, I know that at least 21 of our residents died in other provinces during 1930.

British, European and Other Foreign Persons

In the question of non-resident deaths we must consider also the deaths of foreign persons. During 1930 we registered 21 such deaths: 12 residents of England and Wales, 2 residents of France, 4 of Norway, 1 of Germany and 2 of Italy. Many of these were sailors who died while their ships were in our ports.

Summary of Non-Resident Deaths

A summary of the total number of non-resident deaths in the province during 1930 shows:

(a) Residents of the United States.....	56
(b) Residents of other provinces.....	162
(c) Residents of Great Britain and Europe.....	21
Total.....	239

The total number of residents of Quebec who died elsewhere in the same year were distributed as follows:

(a) In the United States.....	27
(b) In other provinces (incomplete).....	21
Total.....	48

THE VALUE OF CORRECTION

From the Statistical Standpoint

The total number of deaths during 1930 having been 35,954—13.145 per 1,000 population (I am giving three decimal places for the purpose of the following argument), it follows that, if there is to be accuracy, we should exclude the 239 non-resident deaths and, to be logical, include the 48 deaths of our residents who died outside the province. This operation produces a net total of 35,753 deaths, or a death rate of 13.076, a difference of only .069 per 1,000 population. If we drop the decimals, the annual death rate for the province remains at 13.1 in both cases.

From this I conclude that there is not sufficient inaccuracy in the present method of compilation to warrant a change. On the other hand, I must point out that the case might be different in another province, the population of which is smaller but in which as many non-resident deaths might occur. In such a case, the variation in the death rate might approximate 0.3 per 1,000 population. In such a province, attention should be given to non-residents. Generally speaking, however, correction from the statistical standpoint is not important.

From the Civil Registration Standpoint

It sometimes happens that difficulty is encountered when a certificate is needed in the case of a death having occurred outside the territory of residence. If the interchange existed between all the provinces, the applicant would write to the provincial registrar for the certificate and considerable time and correspondence would be saved. The value of correction from the standpoint of civil registration is, therefore, important, and I am convinced that re-allocation among the provinces would be worth while.

Non-Resident Births

The whole question of non-residence is much the same when considered from the standpoint of births, but I have no data on non-resident births, not having given attention to them. The question has its importance, however, especially for those sections of a province that are situated near the provincial boundary on the other side of which, in the adjacent province, is some import-

ant maternity hospital. Registration of births may be made in either province, the one of occurrence or the one of residence. In either case, the registrar in whose office the birth is registered should inform the registrar of the other province.

Correcting Urban Returns in Quebec

Although this paper is concerned chiefly with interprovincial non-residence, I wish to add a few lines on the "internal" aspect of non-residence and to show the plan which we have adopted in Quebec for non-resident urban deaths.

In almost every city and town there is a hospital or other institution to which the population of the district come for treatment. This results in a considerable number of non-resident deaths in such centres. Here the death rate of the community is affected to a far greater extent than that of the province by the inclusion of non-residents. In February last (1931) we had a typical example of this. During the month there had occurred in the city of Westmount 4 deaths of children under 1 year of age; the infant death rate for the city was thus 400.0 per 1,000 living births. In the course of our compilation the 4 infant deaths were later credited to the place of residence, Montreal. The result was that the infant death rate of Westmount became 0.0 while that of Montreal was not much changed, owing to a larger total of births. All this results from the location within the limits of Westmount of the Westmount General Hospital to which Montreal people may go for treatment. Similar cases often happen in any province and the matter certainly deserves attention.

The following reproduction of a page of our monthly Preliminary Report shows how we are trying to solve the problem.

MONTHLY PRELIMINARY REPORT

Total deaths and rate of general mortality in urban centres

Cities and towns of 5,000 pop. and over	Total deaths	Deaths of residents only	Residents dead elsewhere	In hospitals	Crude rate	Adjusted rate
						Deaths of residents only
Urban TOTAL.....	1,616	1,465	105	575	14.3	13.9
Granby.....	15	15	0	0	18.2	18.2
Grand'Mère.....	8	8	1	1	12.3	13.8
Hull.....	33	32	0	7	13.4	12.9
Joliette.....	11	10	2	5	11.1	12.1
Levis.....	28	18	1	14	28.4	19.3
MONTREAL.....	950	889	61	347	14.7	14.7
Lachine.....	27	20	0	14	17.2	12.7
Outremont.....	10	10	4	4.8	6.7
Verdun.....	29	27	12	3	7.0	9.4
Westmount.....	14	8	7	8	7.2	7.7

It will be seen that the first column states the net total of deaths in each city, while the second column gives the total deaths only of resident citizens of each centre who died in that centre; the third column shows the deaths of residents who died elsewhere. The first column establishes the crude death

rate, while the total of the second and third columns gives the corrected rate. For instance, 185 deaths were registered in the city of Quebec during March, 1931—a death rate of 15.6. If, however, we compute only the deaths of citizens of the same city, they number 161—a death rate of 13.6*. I think that our adjusted death rate includes all the necessary corrections.

CONCLUSIONS

Although from the provincial standpoint the correction for non-resident deaths is not an important consideration, the following suggestions are offered, as the question should receive careful and complete study:

1. That the term "non-resident" be clearly defined, the definition to state the length of time a person must spend in a given place in order to become a citizen.
2. That there be appointed a "General Collector" of adequate data concerning non-resident deaths and births in Canada. To him all provincial registrars would transmit copies of non-resident death certificates.
3. That this "General Collector" make a report of his study at the next meeting.

III.—Report of the Committee†

A MEETING of the Committee on Non-resident Births and Deaths was held in Montreal on April 8, 1932, with all the members in attendance.

After due consideration of the difficulties which inevitably would arise in allocation, the following recommendations are submitted:

1. That a system of allocation by residence of all births and deaths is most desirable. Tabulations resulting therefrom should not replace those based on place of occurrence, when appearing in printed annual reports, but should be used supplementary thereto.
2. That, with required co-operation, a system of allocation is feasible with a sufficient degree of accuracy to make it practicable.
3. (a) That the responsibility for drawing up the definitions and rulings essential to a system of allocation should rest with the Dominion Bureau of Statistics.
- (b) Responsibility for administration in effecting an interchange of essential facts should rest with each province.
4. That the "usual place of abode" shall determine residence in the case of death, and in the case of a birth the usual place of abode of the mother shall be taken.
5. That this Committee be continued.

Respectfully submitted:

T. E. ASHTON, *Chairman*

GRANT FLEMING, M.D.

D. V. CURREY, M.D.

W. R. TRACEY

PAUL PARROT, M.D.

*The total of the second and third columns for the urban deaths (1,465+105) does not equal the total of all the deaths; the difference is accounted for by the deaths of rural residents who died in urban centres.

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Can Peroral and Percutaneous Routes Be Used for Vaccination?

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THE non-specific methods of treatment of disease, either by means of foreign protein injections or by physical agents of various sorts, have led to a better understanding of the vegetative nervous system. This form of stimulation therapy has opened up a new field in physiology. As a result of these studies there is available much information that should receive the attention of those interested in public health and preventive medicine. The term "autonomic nervous system" conveys the idea of a part of the vegetative nervous system and has different meanings to pharmacologists and anatomists. The whole of the body machinery entering into processes of adaptation to environment are considered in this communication. The endocrine and hormone apparatus as a whole, the chemical equilibrium of the body, are all concerned in this "neuro-humoral" mechanism of involuntary adjustments of body function. No group of workers should be more interested in how this apparatus of man operates than the people engaged in public health activities. The healthy person may be thought of as one with a well-balanced neuro-humoral controlling system. Adaptation to climate and nutrition, as well as to our parasitic environment, indicates a well-regulated involuntary controlling function. The purpose of preventive medicine is to keep people healthy. The way in which a population can best adapt themselves to their environment extends the scope of preventive medicine and the horizon of this subject extends farther than most of us can see. The biologist, physiologist and the biochemist occupy positions of equal rank with the bacteriologist and immunologist.

The control of communicable disease has been based upon two fundamental methods: first, restriction of the distribution of the causative agent and, second, increasing the resistance of the host. The first method has been the more successful. The whole sanitary science as now carried out—water purification, sewage disposal, milk pasteurization, food handling, as well as air conditioning of living, working and assembling quarters—can be cited as practical applications of the principle of restricting the distribution of disease-producing bacteria and viruses. The second principle, increasing the resistance of the host, has not been so successful in its practical application. The reason for this is that it has been necessary to introduce the antigen for active immunization by skin puncture. This has been associated with an inflammatory reaction and accompanied by the variable and abnormal systemic responses to a foreign protein intoxication. The protective value of vaccination against smallpox, diphtheria and typhoid has been proved. There are many obstacles to be overcome if an active immunization procedure is applied effectively in a civilian population.

Recent Investigations

Peroral, percutaneous and such attempts to introduce an antigen to increase resistance of the host and avoid an inflammatory reaction are receiving

more and more attention. There is a real need for such methods in public health work. The experienced bacteriologist and immunologist considers that the subcutaneous method has proved its value and hence should be recommended. He does not recognize and is not familiar with the practical difficulties of the application of such methods when applied to several thousand or even to several million people.

The peroral and percutaneous route of introducing a vaccine may be regarded from a new angle in the light of some recent investigations. Using an automatic pump, Petersen, Mueller and Boikan (1) injected dilute suspensions of bacteria intravenously in dogs over long periods of time. At the beginning of the injection there were no demonstrable changes in body function. The reticulo-endothelial system removed the bacteria from the circulating blood. The fixation or phagocytosis of the living bacteria was not associated with evidence of toxic symptoms or disturbed autonomic nervous system balance. This latent or first phase was followed by a second phase characterized by stimulation. There was (1) splanchnic vasodilatation, (2) splanchnic leucocytosis, (3) increase in lymph proteins (increase in permeability of liver cells), (4) mobilization of sugar from stored glycogen, (5) increased phagocytosis by the reticulo-endothelial system. The first or latent stage initiated the second or stimulation stage by liberating foreign proteins from the fixed bacteria within the reticulo-endothelial system. The presence of bacteria in the blood stream was not associated with evidence of changes in body function. It was only after these bacteria were phagocytized by fixed endothelial cells and disintegrated by intra-cellular digestion that body changes could be demonstrated. These observations have a bearing upon the problem of peroral or percutaneous vaccination, as will be shown later.

There seems to be a certain correlation in the functional status of the various physiological systems of the body. When one large organ group is in a very active state of function, some other large physiological unit decreases its functional activity during the same period of time. The active hyperaemia, the increase in oxydation and the increase in the by-products of metabolism of physiologically active tissues, such as the stomach, small intestine, liver, pancreas, etc., during digestion are well known. The size of the lumen of capillaries determines to a great extent the distribution of the blood supply. If the capillaries in a certain organ become filled with blood, which is associated with secretion or activity, one sees many more capillaries than when this organ is in a resting state. The capillaries seem larger as well as more numerous. The number of leucocytes per cubic millimetre of blood are increased in such dilated capillary plexuses in physiologically active tissue. Mueller and Petersen (2) showed that the activity of the splanchnic region following the ingestion of food differed only in the degree of stimulation and was comparable to that found after subcutaneous injection of a foreign protein, as well as after bacterial infections. In other words, the splanchnic system of the body—that is, the gastro-intestinal tract and its glandular appendages with their associated blood and lymph channels—can be stimulated in a purely physiological way (ingestion of food); also, this system can be caused to manifest increased activity after certain foreign substances are injected into the body. The degree of toxicity or the relative stimulating action of the injected material, as well as the amount and the place where it is introduced, all influence the activity of the splanchnic region. Nedzel and Arnold (3) showed that bacteria pass through the wall of the intestinal tract and can be shown to be present in the splanchnic organs under normal conditions. Fisher (4) showed yeast to be absorbed from the small intestine and also from the large intestine. The intestinal mucosa is not an impermeable membrane, but is ordinarily a permeable body covering and the reticulo-endothelial network within the splanchnic region is the real barrier against systemic invasion. The second or stimulation phase brought out by Petersen and his co-workers is not present under normal conditions. The enteric bacterial flora

are not foreign to the splanchnic vascular and lymph circulating fluids. They are fixed by the reticulo-endothelial cells and the proteins liberated are not foreign so long as the enteric bacterial flora is of normal composition or consists of the endogenous forms. But if certain exogenous or foreign bacteria, such as *B. typhosus*, *B. dysenteriae* and some of the animal paratyphosus B or enteritidis groups, are absorbed along with the endogenous flora, the stimulation phase, so well demonstrated by Petersen, becomes apparent and manifestations of systemic intoxication are in evidence. Bacteria enter the splanchnic circulation by passing through the mucosa of the enteric tract. This process is physiological as long as the absorbed living bacteria belong to the endogenous flora residing within the lumen of the tract. The reticulo-endothelial system within the splanchnic blood and lymph channels has plenty of experience and an excellent opportunity to become an efficient phagocytizing agent. They are the safeguards placed between the intestinal wall and the body cells.

PERORAL AND PERCUTANEOUS IMMUNIZATION

Peroral

Returning to the problem of active immunization from a practical public health standpoint, the application of the antigen to a body surface would be an ideal method. The oral route would meet with the least resistance when applied to a large group of the population. It would be theoretically necessary to cause a period of stimulation after the antigen has passed through the enteric body surface and has been fixed in the splanchnic reticulo-endothelial system. If this second phase was not brought about, the reaction would be the same as that just mentioned regarding the endogenous flora. The bacteria would be phagocytized, digested if not too numerous, passed on into the biliary duct system if larger numbers are engulfed than can be lysed and proteolysed. No abnormal body reaction would follow and nothing would remain to indicate a previous experience with these bacteria.

Arnold (5) showed that bile and fresh egg white introduced in the lumen of the duodenum in the post-digestive animals caused a change in the equilibrium of the vegetative or autonomic nervous system. Kaufmann (6), Nedzel, Stonecipher and Arnold (7) have shown that dilute solutions of saponin also cause changes in the autonomic functional status. These are examples of substances applied to the splanchnic body surface (mucosa of the alimentary tract) which cause a stimulation of the autonomic or neuro-humoral apparatus approximating that described by Petersen in connection with changes in permeability, blood chemistry, etc.

Percutaneous

Many attempts have been made to use the percutaneous route for the introduction of a vaccine or an antigen. Local applications have been made on the skin surface of dissolved and soluble bacterial products, such as those produced by the transmissible lytic agent of d'Herelle and the autolysates produced after longer incubation as suggested by Besredka. There is little evidence that the bacteriophage of d'Herelle or the antivirus of Besredka play any part in this reaction. It seems much more likely that we have at our disposal a new physico-chemical bacterial protein preparation.

Viable bacteria placed upon the skin rapidly disappear from the intact skin surface (Arnold, 8). Evaporation and possibly absorption of fluids are the first demonstrable reactions when bacteria are suspended in aqueous medium in contact with the skin. Bacteria are in this way brought in direct contact with the cornified layer of the skin.

After contact with these cells the bacteria cannot be cultured and cannot be found by sectioning and staining the skin. When bacteria are absorbed into leather, silk, cellulose or cotton and wood, they can be recovered in viable form from such substances. If bacteria are suspended in such fluids they are absorbed into the matrix of the porous materials along with the fluid. But if aqueous suspensions of bacteria are placed on the skin and after 30 minutes pieces of the skin are removed and cultured, no viable bacteria can be demonstrated. When inert objects, as mentioned above, are examined, up to 90 per cent of the bacteria can be recovered in a viable state after they have disappeared from the surface.

The introduction of an antigen by the percutaneous route is a possibility, but this port of entry seems to be less adaptable than the enteric route. The clean, intact, normal skin controls the bacterial flora on its surface by destroying the exogenous forms. Under ordinary circumstances, the protective and defensive action of the epidermis offers a barrier against the introduction of antigenic substances by this route. Mechanically introducing the antigenic material into the spaces in the hair sheaths, as in mercury inunctions, used by Loewenstein for diphtheria immunization, offers a new field of investigation. Based on our past experience and reasoning from the observations recorded in literature, one will have to prepare in some way the host for the antigenic reception, similar to the stimulation phase described by Petersen.

Discussion

The seasonal changes in metabolism can be correlated with alterations in susceptibility to certain diseases (Stallybrass, 9, and De Rudder, 10). The age and sex differences in susceptibility are beginning to be considered as results of metabolic processes of the particular groups. These changes are to a considerable extent the results of alterations in the vegetative nervous system. The sympathetic and parasympathetic nervous systems, with the endocrine secretions and hormones, are a part of the neuro-humoral adjusting mechanism to environmental stimuli. The practical application of active immunization by the peroral or percutaneous routes will depend on accompanying the local application with stimuli of sufficient intensity to increase cell permeability and cause increased resistance as a result of this experience. If the stimuli are of the same intensity as brought about by subcutaneous injection of a foreign protein (vaccines), then an intoxication of the magnitude of an inflammatory reaction is produced; hence there would be no advantage enjoyed by such methods. In other words, the ideal would be to introduce the vaccine through an intact and normal body surface covering and then stimulate the body enough to produce a reaction similar to the stimulation phase (Petersen), but not of sufficient intensity to be compared to an inflammatory reaction.

McDaniels (11) substantiated Ross's (12) oral immunization experiments with pneumococcic vaccine in rats. When fresh egg white was administered along with the pneumococci-autolysate the protection enjoyed by the animals against intraperitoneally injected multiple lethal doses was more regular, and little variation was observed between different animals. We explained this upon the stimulation caused by applying fresh egg white to the enteric mucosa and consequently the antigen absorbed into the splanchnic circulation was in contact with cells which were in a more permeable state.

Active immunity following a naturally acquired infection or resulting from subcutaneous injections of the specific foreign protein is closely associated with the stimulation of the body cells. This stimulation is not specific; the presence of the antigen at the time of the metabolic and autonomic alterations of function is the important factor. Fisher

(4) has shown that yeast introduced into the large intestine of dogs and rats is absorbed and can be demonstrated in the splanchnic organs by cultural methods. When fresh egg white is administered by mouth and yeast by rectum, larger numbers of yeast cells can be cultured from the splanchnic organs. The egg white in contact with the upper enteric mucosa stimulates the body (Arnold, 5), and a short but definite period corresponding to the stimulation phase (Petersen) can be demonstrated. Saponin is a much stronger irritant or stimulant than fresh egg white. Bile is a weaker stimulant (only after intra-gastric administration in the fasting state) than egg white. Heat-killed meat cultures of *B. enteritidis* yield a stable but strong gastro-intestinal irritant, (Arnold, 5). The use of bile has been advocated by Besredka, although he has assumed a desquamating action of the bile upon the intestinal mucosa. The changes in intra-intestinal acid-base equilibrium and bacterial flora produced by the ingestion of bile during the fasting state have been dealt with in another place (Arnold, 5). The action of bile is not due to its damaging action on the mucosa of the small intestine. We have substantiated the observations of Boone, Chase and Brink (13) that slight mechanical abrasions to the duodenal mucosa do not increase the demonstrable number of viable bacteria passing through the wall of this segment of the intestine.

Mention should be made of the possibility of increasing the resistance of the host to disease by applying the causative agent in the form of a vaccine on a body surface without a demonstrable antibody production as determined by the usual methods. This question is too involved to discuss here. Antibodies are produced after a period of stimulation of the body at the time some antigenic substance is in contact with the cells. This raises the question of the influence of the inflammatory reaction upon demonstrable antibody production in the blood. Closely associated with this is the question of the relationship between antibody titre and resistance to infection. Discussion of these questions would, of course, be out of place in this short article.

Method of Peroral Vaccination

The literature on oral vaccination has been brought up to date and the experimental work done in this laboratory has been summarized (Finder and Simons, 14). One gram of dessicated ox bile on an empty post-digestive stomach (preferably early in the morning), is swallowed with the aid of 100 cc. of warm water. There will be a period of from one to two hours during which the stomach will not secrete hydrochloric acid. After thirty minutes, the typhoid vaccine is administered. We have used three different forms of this preparation. One was a pill which contained one billion dried and heat-killed *B. typhosus*; one was 1 cc. of the usual fluid vaccine in a glass of warm water; another form was a lysed *B. typhosus* culture with phage. The dosage in the latter was more difficult to standardize. After growing *B. typhosus* for eight hours in broth and potent dose of lytic agent (phage) added, the flask was incubated overnight or until it was clear. This was usually overnight if it cleared at all. The development of resistant strains of *B. typhosus* to phage is not understood. We have discarded flasks that did not clear after 48 hours incubation. Lysis and growth are in progress during the time of incubation after phage has been added. Hence it is impossible to standardize the lysed *B. typhosus* culture in terms of vaccine dosage. The cleared or lysed culture is passed through a Berkefeld filter to remove undissolved viable bacteria. We have used from one to five cubic centimetres in a glass of warm water. The majority of our cases were given two cubic centimetres.

The purpose is to introduce the antigen by mouth during the time the gastric acidity is depressed by the action of the bile. The bile must not be

more than a 3 per cent solution or it may have an irritating or toxic effect and cause free acid secretion. The mechanism of the splanchnic reactions following the oral administration of dilute solutions of bile has been dealt with in greater detail in a previous paper (Arnold, 5). The bile and the antigen have been administered on three successive mornings in our experiments. A group of 61 humans showed agglutination in the serum after three weeks. The titre ranged from 1:40 to 1:320. All showed the presence of *B. typhosus* agglutinins. Ruge (15) has recently recorded a well controlled experiment of oral vaccination compared to subcutaneous injection. The agglutinins against *B. typhosus* were higher in the orally vaccinated group after 5 months than in the subcutaneously vaccinated series.

Every attempt has been made to analyze some of the factors involved in peroral and percutaneous vaccination procedures. We have had some experience in experimental methods that may aid in understanding the principles involved in these procedures. It is hoped that students of preventive medicine and workers in public health will be stimulated to examine critically the possibility of using the enteric tract as a route for the administration of a vaccine.

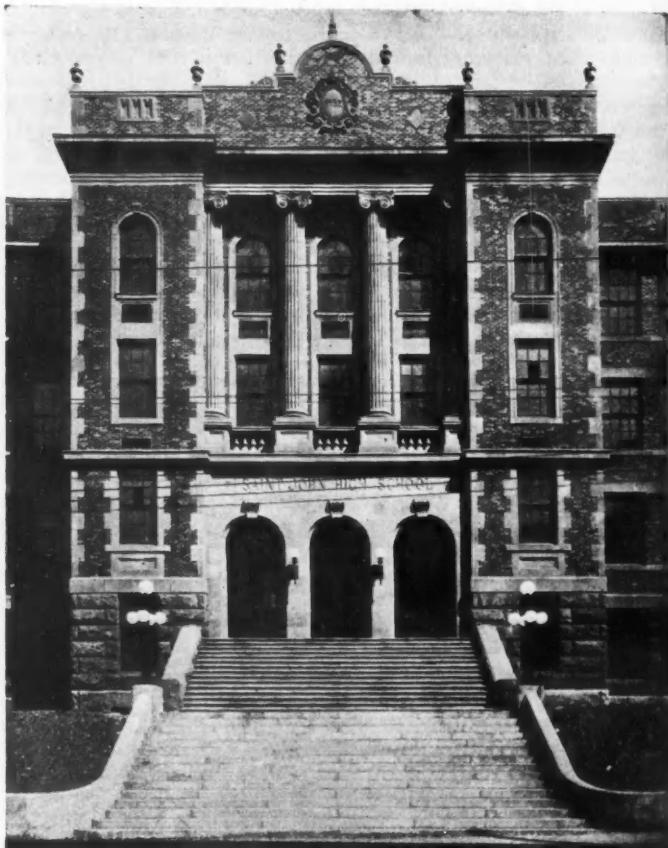
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Twenty-Second Annual Meeting

SAIN^T
JOHN

JUNE
19th
TO
21st



SAINT JOHN HIGH SCHOOL, CONVENTION HEADQUARTERS

In these difficult days of reduced appropriations and increasing responsibilities, in what better way can we aid in the solution of our public health problems than by gathering together and exchanging helpful ideas? Once again we urge our members, especially those in the eastern provinces, to make every effort to be present at our twenty-second annual meeting, the first to be held in Saint John since 1922.

Perhaps more than at any other time in recent years is an expenditure for travel to the annual meeting justified. Remember, both you and your community will benefit from your attendance and the stimulus and encouragement given and received will do much to advance the cause of public health in Canada.

WM. WARWICK, M.D., D.P.H.

Programme Features

TWO of the most important health problems which concern every citizen of Canada are the problems of tuberculosis and cancer. It is fitting, therefore, that the Association in convention should be addressed on these subjects not only by those in Canada who are leading in the efforts to control these diseases, but also by internationally known representatives of the medical profession in Great Britain and the United States. The general session on Monday afternoon will consider the subject of cancer. The Hon. J. M. Robb, Minister of Health for Ontario, and the Hon. G. H. Murphy, Minister of Health for Nova Scotia, will present the plans that are being followed in their provinces. Dr. Joseph Colt Bloodgood, of Johns Hopkins University, Baltimore, and known throughout the continent as one of the leading authorities, will summarize the present position in regard to this disease.

The addresses of the Honorary President and the President will also be features of this session.



SIR HUMPHRY ROLLESTON
Cambridge, England.

Ontario and New Brunswick will be outlined by Dr. F. C. Middleton, Deputy Minister of Health, Saskatchewan, Dr. W. J. Bell, Deputy Minister of Health, Ontario, and Dr. R. J. Collins of Saint John.

One of the addresses of special interest at this session will be a résumé of the work of the Health Organisation of the League of Nations by Dr. J. G. Fitzgerald, Dean of the Faculty of Medicine and Director of the Connaught Laboratories and School of Hygiene of the University of Toronto.



DR. JOSEPH COLT BLOODGOOD
Baltimore, Maryland.

On Tuesday afternoon new aspects of the control of tuberculosis will be presented by two eminent physicians from Great Britain, Sir Humphry Rolleston, ex-Regius Professor of Physic in Cambridge University, and Col. Lyle Cummins, Professor of Tuberculosis in the Institute of Public Health, Cardiff, Wales. The session will also record the remarkable results obtained in Canada by the provincial and municipal departments of health.

The achievements in Saskatchewan,



COL. S. LYLE CUMMINS
Cardiff, Wales.

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THE PREPARATION AND USE OF SCARLET FEVER TOXOID

THE protection of children against scarlet fever by active immunization with streptococcal toxin has been much impeded because no clear distinction can be drawn between the quantity of toxin required to immunize the more refractory individuals and the quantity which produces undesirable reactions in those most susceptible to its toxic effects.

It appears to be a general principle that prolonged contact with formalin results in a marked reduction of specific toxicity without a corresponding loss of antigenic potency. This effect has been observed in a number of toxins with widely differing specific properties such as tetanus, dysentery, perfringens, botulinus and staphylococcus toxins, snake venom and abrin.

The detoxifying effect of formalin was first reported in 1909 by Löwenstein who obtained tetanus toxoid capable of immunizing guinea-pigs. It was not until 1923 that immunization of children against diphtheria was introduced by Ramon, although Glenny and Südmerson in 1921 had immunized guinea-pigs with toxoid.

Similarly, scarlet fever toxoid was produced by Zoeller in 1925 and used by Sparrow and Celarek in 1927 for the active immunization of children.

It is noteworthy that Zoeller and Manoussakis purified their toxoid by precipitation with acetic acid, and that immunization with toxoid purified in the same way and concentrated by precipitation with alcohol was carried out on a large scale by Ando and Ozaki in 1930. These investigators reported that of 1,187 susceptible children treated with concentrated toxoid, 82 per cent became Dick negative.

Most of those who have attempted to produce scarlet fever toxoid have experienced considerable difficulty in obtaining material sufficiently detoxified for human use without having recourse to methods which result in the loss of antigenic potency. This is in harmony with the comparative stability of scarlet fever toxin in relation to aging, heat, light and other agents which are injurious to most bacterial

toxins. There is a good deal of evidence that this stability depends, at least in part, on the total nitrogen content of the medium containing the toxin.

The report of Veldee on the use of toxoid concentrated by precipitation with acetone marks another advance towards an immunizing agent for scarlet fever with which one may hope for a reasonable degree of immunization without the disadvantage of an unduly long series of doses on one hand, and on the other of a high proportion of local or general reactions following its administration.

Frieda H. Fraser.

TUBERCULOSIS WEEK, TORONTO, JUNE 26TH

THE meeting of the National Tuberculosis Association with the Canadian Tuberculosis Association, the American Sanatorium Association and the Tuberculosis Secretaries in Toronto during the week of June 26th will make one of the most important events in Canadian tuberculosis history. And tuberculosis history forms a large part of the history of medicine, of preventive medicine, of public health. As tuberculosis stands to-day our chief killing disease before the age of fifty, and is therefore our greatest public health problem, physicians, nurses and public health officials should take full advantage of the opportunity presented of attending the sessions of the conference and learning first-hand the new points of those most actively engaged in tuberculosis on the continent. Such an opportunity comes but rarely.

The Canadian Public Health Association warmly welcomes the visiting associations and their distinguished guest speakers, Sir Humphry Rolleston, chairman of the famous Papworth Tuberculosis Colony and until recently Regius Professor of Physic at Cambridge, and Col. S. Lyle Cummins, Professor of Tuberculosis in the Institute of Preventive Medicine and Director of Research to the King Edward VII Welsh National Memorial Association, Cardiff, Wales. The fine programme, a synopsis of which appears herewith, in itself should ensure success for the Tuberculosis Week, Toronto, June 26th.

Opening General Meeting, Tuesday, June 27, 8.30 p.m.

Address of the President, Dr. John H. Peck, Des Moines; Report of the Managing Director, Dr. Kendall Emerson, New York; Award of the Trudeau Medal; Report of the Committee on Nominations; Reception and Dance.

CLINICAL SECTION

Wednesday, June 28, 9.30 a.m.

BONE AND JOINT TUBERCULOSIS IN ADULTS—R. I. Harris, Toronto.
OLEOTHORAX, END RESULTS AND DANGERS—Ray Matson, Portland, Oregon.
MALIGNANCY OF LUNGS AND PLEURA—Louis Hamman, Baltimore.
COLLAPSE THERAPY—H. D. Chadwick, R. C. L. Marke and Joseph Thomas, Detroit.

Thursday, June 29, 9.30 a.m.

GENITO-URINARY TUBERCULOSIS—David W. MacKenzie, Montreal.
MEDIASTINAL DISEASE—B. R. Kirklin, Rochester, Minn.
BRONCHIAL STENOSIS—Leo Eloesser, San Francisco.
THE INDIAN AND HOME PREVENTION—G. R. Ferguson, Fort San, Sask.
LEUCOCYTE COUNT DURING PNEUMOTHORAX TREATMENT—John K. Deegan, West Haven, Conn.

PATHOLOGICAL SECTION

Wednesday, June 28, 2.00 p.m.

Symposium, THE BACTERIOLOGY OF ACID-FAST STRAINS:
 PATHOLOGY OF R AND S TUBERCLE BACILLI—S. A. Petroff, Trudeau, N.Y.
 ORGANISMS IN SKIN NODULES OF TUBERCULIN-REACTING CATTLE—L. L. Daines,
 Salt Lake City.
 STOOLS OF TUBERCULOUS CHILDREN—Henry Stuart Willis, Northville, Mich.
 THE DEVELOPMENT CYCLE—Morton C. Kahn, New York.

Thursday, June 29, 2.00 p.m.

(Joint session with the Clinical Section)

Symposium, SILICOSIS AS AN ETIOLOGICAL FACTOR:
 THE PREVALENCE OF SILICOSIS AND ITS EFFECT—Anthony J. Lanza, New York.
 OCCUPATIONAL HISTORY—R. R. Sayers, Washington, D.C.
 CLINICAL ASPECTS OF SILICOSIS AND SILICO-TUBERCULOSIS—A. R. Riddell,
 Toronto.
 DEVELOPMENT OF THE SILICOTIC NODULE—Willis S. Lemon, Rochester, Minn.
 ROENTGENOLOGICAL ASPECTS—Henry K. Pancoast, Philadelphia.
 TITLE TO BE ANNOUNCED—Col. S. Lyle Cummins, Cardiff, Wales.
 DISCUSSION—J. C. Meakins, Montreal; J. G. Cunningham and R. M. Price, Toronto.

Friday, June 30, 9.30 a.m.

Report of the Committee on Medical Research.

MOTION PICTURE OF ACID-FAST BACILLI—R. W. G. Wyckoff, New York.
 BIOLOGY OF THE TUBERCLE BACILLUS—H. B. Richardson, E. Shorr and R. O. Loebel,
 New York.
 ANTIGENIC PROPERTIES OF TUBERCULIN PROTEIN AND ITS MOLECULAR CONSTITUITION—Florence B. Seibert, Philadelphia.
 TUBERCULO-PROTEIN MA-100 AND OLD TUBERCULIN—Joseph D. Aronson and Rae V.
 Nicholas, Philadelphia.
 CELLULAR REACTIONS TO TUBERCULO-PROTEIN—F. R. Sabin and K. C. Smithburn,
 New York.
 PRECIPITIN REACTING WITH PHOSPHATIDES FROM HUMAN, BOVINE, AVIAN AND
 LEPRAE BACILLI—Ernest S. Mariette, Oak Terrace, Minn.
 REPORT ON TUBERCULO-PROTEIN MA-100—John Reichel, Philadelphia, and Jessamine S.
 Whitney, New York.
 DISCUSSION—Esmond R. Long, Philadelphia.

Friday, June 30, 2.00 p.m.

HEMATOGENEOUS PULMONARY TUBERCULOSIS—James Alexander Miller, New York.
 LYMPHOCYTES IN PULMONARY TUBERCULOSIS—B. K. Wiseman and C. A. Doan, Columbus, O.
 ROENTGENOLOGICAL FINDINGS IN NON-SENSITIZED AND SENSITIZED RABBITS—
 Hugh E. Burke, Ray Brook, N.Y.
 TUBERCULIN REACTION IN CHILDHOOD—J. A. Johnston, Detroit.
 MANTOUX TEST WITH THE MA-100 TUBERCULIN—E. Rosencrantz, San Francisco.

SOCIOLOGICAL SECTION

Wednesday, June 28, 2.00 p.m.

Symposium, VARIED METHODS OF CASE-FINDING:
 ORGANIZING—Samuel O. Pruitt, Philadelphia.
 CLASSIFYING—Theodore J. Werle, Lansing, Mich.
 REDUCING THE COST—Herbert R. Edwards, New Haven, Conn.
 IN THE UNEMPLOYED—Margaret Witter Barnard, New York.
 Symposium, THE ROLE OF THE PRIVATE PHYSICIAN IN THE PRE-SCHOOL EXAMINATION
 OF CHILDREN:
 THE HEALTH OFFICER'S POINT OF VIEW—Henry F. Vaughan, Detroit.
 THE SCHOOL PHYSICIAN'S POINT OF VIEW—John T. Phair, Toronto.
 THE TUBERCULOSIS ASSOCIATION'S POINT OF VIEW—Charles S. Prest, Brooklyn, N.Y.

Thursday, June 29, 9.30 a.m.

TUBERCULOSIS, A FAMILY DISEASE:
 EPIDEMIOLOGICAL ASPECTS—J. A. Myers, Minneapolis, Minn.
 EVOLUTION—C. A. Stewart, Minneapolis, Minn.
 TWO BEDS PER DEATH—Henry D. Chadwick, Detroit.
 CARE OF TUBERCULOUS CHILDREN—John B. Hawes, Boston.
 SOCIAL ASPECTS—Edward Hochhauser, New York.

Friday, June 30, 9.30 a.m.

THE PHILOSOPHY OF HEALTH EDUCATION—Ira V. Hiscock, New Haven, Conn.
 AUTHENTICITY OF MATERIALS—W. W. Bauer, Chicago.
 TOOLS OF THE HEALTH EDUCATOR—Grant Fleming, Montreal.

LABORATORY SECTION

*A Comparison of Methods for the Determination of Milk Solids**

A. R. BONHAM, B.A.Sc.

Division of Laboratories, Department of Health, Ontario

THE content of solids in a milk is an indication of its quality; hence one finds that various governments endeavour to safeguard their milk supply by the enactment of regulations stating the minimum amount of these milk solids that must be present. In Ontario we have the Milk and Cream Act which stipulates that no milk shall be sold in the province, for human consumption, which contains less than eleven and three-quarters per cent of total solids. Any person violating this provision of the Act is liable to prosecution and fine.

It is needless to say that in such prosecutions the analytical report would be considered important by both the prosecution and the defence; hence the analyst might reasonably expect to be closely questioned concerning the method of determination used by him in the analysis of the milk in question.

In order that we might be better informed concerning the common methods used in determining the total solids of milk, especially with respect to their comparative accuracy, certain experimental work was conducted by us. This consisted in carefully determining the total solids in several samples of milk by four different methods. The methods used were as follows:

(a) By evaporation in a vacuum oven.

- (b) The official method of the American Public Health Association.
- (c) The acetone method.
- (d) The calculation method of Hehner and Richmond.

Brief details of these, together with the respective results obtained by their use, are now given.

Vacuum Oven Method

In this method, as also in the A.P.H.A. and acetone methods, the determinations were made in duplicate and the amount of milk used for the tests was from 2.5 to 4.0 grams. The samples were evaporated in flat-bottomed glass dishes 5 centimetres in diameter.

When milk is evaporated to dryness in a vacuum oven, some frothing takes place at a certain stage of the procedure, and if the milk happens to be in a shallow dish, such as used for milk solids' determination, some of the sample is likely to froth over the side, thereby introducing an error. To make sure that this did not occur, the samples, as soon as weighed, were evaporated on the water bath for thirty minutes, at the end of which time the greater portion of the water in the milk had been removed. We found that samples so treated might then be transferred to the vacuum oven and heated under a vacuum without fear of frothing. The oven was

*Presented before the Laboratory Section of the Canadian Public Health Association, at the 21st Annual Meeting, Toronto, May, 1932.

maintained at a temperature of 70° to 72°C. and under a high vacuum for two hours. After this the samples were placed in a desiccator and, when cool, were weighed. To ascertain whether or not there had been a complete removal of the water from the milk, the dishes were again placed in the oven and heated under a vacuum as before, except that the length of time was reduced from two hours to one. This procedure was continued until two consecutive weighings checked closely, which invariably happened after two or three heatings. Table I shows the results obtained from duplicate determinations with ten different milks when this method was used.

TABLE I
Per Cent Total Solids in Milk by
Different Methods

Lab. No.	% Fat	Vacuum Oven	A.P.H.A.	Acetone	Hehner Calculation
610	3.10	11.49	11.36
		11.48	11.39		
613	3.20	11.71	11.41
		11.66	11.61		
607	3.95	12.61	12.41	12.63
		12.60	12.46		
665	2.10	10.59	10.54	9.01
		10.69	10.53		
698	3.65	12.30	12.10	12.06	12.27
		12.23	12.08	12.06	
771	1.90	10.02	9.92	9.85	9.92
		10.04	9.90	9.83	
H.F. 4.60	13.79	13.57	13.55	14.66	
		13.69	13.57	13.56	
L.F. 1.10	9.90	9.65	9.88	9.83	
		11.17	9.73	9.83	
842	3.80	12.39	12.13	11.97	12.45
		12.36	12.11	12.00	
830	3.20	11.58	11.42	11.45	11.48
		11.59	11.17	11.45	

The film or skin which forms on the surface of milk during evaporation might be expected to retard somewhat the rate of removal of water from a sample, so some tests were made to ascertain whether the elimination of this film by the use of sand in the dish, or by the addition of one cubic centimetre of acetone to the milk, would make it possible to remove all of the water from the solids in two hours and thus somewhat expedite the determination. The results obtained in this investigation are shown in Table II and they indicate that the use of these substances made practically no difference to the determination.

TABLE II

Results of Variations in Vacuum Oven Method					
Lab. No.	% Fat	Weight of Milk	Weight of Solids	Hours in Vacuum Oven at 72°C.	Method
774	3.60	2.5288	0.3100	2	Acetone added
			0.3094	3	
			0.3091	4	
2.5276		0.3112		2	
		0.3102		3	
		0.3098		4	
2.5422	0.3119		0.3106	2	Sand used
			0.3106	3	
			0.3106	4	
2.5244	0.3118		0.3102	2	
			0.3102	3	
			0.3102	4	
2.5150	0.3116		0.3102	2	Nothing added
			0.3098	3	
2.5141	0.3112		0.3092	2	
			0.3088	3	
			0.3088	4	
830	3.20	2.5206	0.2914	2	Acetone added
			0.2901	3	
			0.2904	4	
2.5354	0.2930		0.2914	2	
			0.2914	3	
			0.2914	4	
2.5288	0.2910		0.2910	2	Sand used
			0.2908	3	
2.5223	0.2918		0.2900	2	
			0.2904	3	
2.5137	0.2930		0.2913	2	Nothing added
			0.2913	3	
2.5004	0.2910		0.2896	2	
			0.2897	3	
			0.2897	4	

The American Public Health Association Method

This is the official method of the A.P.H.A. for the determination of total solids in milk. It is likewise that of the Association of Official Agricultural Chemists. Briefly, it directs that 3 to 5 cc. of milk be pipetted into a flat-bottomed dish of not less than 5 cm. diameter, weighed quickly and then heated at the temperature of boiling water until it ceases to lose weight.

In our determinations using this method, the milk was evaporated on a water bath until the first two consecutive weighings agreed closely. The loss by evaporation from weighing the milk in open dishes and the error resulting therefrom were avoided by covering the dish with a counterpoised watch glass. Some tests were made to ascertain exactly what this loss from evaporation during the weighing actually amounted to, and in Table III are shown the results obtained from ten tests. In each of these a dish containing a sample of milk was left un-

covered for two and three minutes respectively. These periods of time were selected because we found that the average time required for us to weigh accurately a sample of milk for a total solids' determination approximated three minutes.

TABLE III
Loss Weighing Milk in Uncovered Dish

Milk No.	Per Cent Fat	Loss in Grams 2 Minutes	Loss in Grams 3 Minutes
771	1.90	0.0117 0.0104 0.0102	0.0175 0.0162 0.0154
698	3.65	0.0080	0.0114
H.F.	4.60	0.0064 0.0076	0.0096 0.0116
L.F.	1.10	0.0085 0.0074 0.0074 0.0070	0.0127 0.0110 0.0118 0.0100
Average		0.0085	0.0127

In addition, weighings were made to ascertain the amount of moisture which is absorbed by dry milk solids when they are weighed in uncovered dishes. These tests consisted of taking carefully weighed, dry solids from the desiccator, exposing them to the moisture of the atmosphere for three minutes and then re-weighing them. Some solids, when so treated, failed to show any increase in weight, while a few gained by such a small amount that for practical purposes it might be considered as negligible.

In Table I will be found the results obtained from duplicate determinations of solids in ten different samples of milk by the A.P.H.A. method and in Table IV the extent to which these vary from the vacuum oven method when used on the same samples.

TABLE IV

Per Cent Variation from Vacuum Oven Method					
Lab.	% Total Solids	% Vacuum	A.P.H.A.	Acetone	Hehner Calculation
No.	Fat	Oven			
610	3.10	11.48	-0.11
613	3.20	11.68	-0.17
607	3.95	12.60	-0.17	+0.03
665	2.10	10.64	-0.11	-1.63
698	3.65	12.26	-0.17	-0.20	+0.01
771	1.90	10.03	-0.12	-0.19	-0.11
H.F.	4.60	13.74	-0.17	-0.19	+0.92
L.F.	1.10	10.03	-0.34	-0.18	-0.20
842	3.80	12.37	-0.25	-0.39	+0.08
830	3.20	11.58	-0.29	-0.13	-0.10
Average		-0.19	-0.21	-0.21	-0.21

The Acetone Method

This method calls for an addition

to the sample of milk, immediately after it has been weighed, of one cubic centimetre of acetone and then the placing of the dish with its contents on a rapidly boiling water bath where it is left for thirty minutes. After this it is removed, wiped dry, placed in a water oven and heated for one hour, following which it is cooled in a desiccator and weighed.

By the foregoing method we made duplicate determinations with six different milks and the results obtained therefrom are shown in Table I, while the per cent variation of these figures from those arrived at with the same milks by means of the vacuum oven will be found in Table IV.

The Calculation Method of Hehner and Richmond

It has been shown by Hehner and Richmond and others that if one knows the specific gravity and the per cent butter fat of a milk, it is possible, by means of a formula, to calculate the per cent of its total solids. Such formulae have been worked out by several investigators but we have used only the one proposed by Hehner and Richmond, which is as follows:

$$T = 0.25S + 1.2F + 0.14$$

where T is the per cent of total solids, S the lactometer reading and F the per cent of fat.

In our determinations of total solids by this method we used a Quevenne lactometer, the accuracy of which was checked by a pycnometer and the per cent of butter fat was ascertained by means of the Babcock test.

Table I gives the per cent of total solids for eight different milks when the Hehner and Richmond formula was used and Table IV shows the per cent these results vary from those obtained by the vacuum oven method.

Summary

1. To overcome the loss of weight during the weighing of the milk, it is advisable to cover the dish with a watch glass.

2. The vacuum oven method for determining milk solids was found to give

slightly higher results than either the acetone or the American Public Health Association method.

3. The calculation method of Hehner and Richmond should not be considered an accurate means of determination but rather a rapid, practical one which gives approximate results.

References

- (1) American Public Health Association. Standard Methods of Milk Analysis, 5th Ed., p. 49.
- (2) Allen. Commercial Organic Analysis, 4th Ed., v. VIII, p. 148.
- (3) Leach. Food Inspection and Analysis, 4th Ed., p. 138.

PUBLIC HEALTH ENGINEERING

The May Meeting

THE annual meeting of the Public Health Engineering Section was held this year in the Royal York Hotel, Toronto, on May 16th and 17th. The group met at the same time as the Ontario health officers and the meeting was quite successful. It opened with a luncheon on the 16th in the library of the hotel. This was well attended and served as a "get-together" for the engineers. Following the luncheon, Commissioner R. C. Harris, Toronto, spoke on the activities of the engineer, stressing his contributions to public health advances and the responsibilities he is called upon to assume in community life. Dr. W. J. Bell, Deputy Minister of Health, Ontario, eulogized the work of the engineer in public health and pointed to other branches in which lay opportunities for engineering service.

The afternoon session of the opening day was devoted to three papers and the business of the Section. Dr. G. G. Nasmith presented an interesting paper on what becomes of sewage discharged into surface waters. In this he made clear what natural agencies are at work, to what extent these can be utilized, and the danger of undue pollution in natural waters. The second paper dealt with cross-connections in public water supplies and was prepared by Messrs. Burn and

Johnston of the Ontario Department of Health. The paper was a comprehensive one, reviewing what has been accomplished and pointing to dangers in many unexpected places. The final paper, prepared by Mr. Howard and Dr. Berry, dealt with algal nuisances in surface waters. This outlined the conditions under which algae may produce offensive odour conditions in waters and described a number of such experiences in Ontario and elsewhere, particularly at Mimico, where litigation had taken place.

The following officers were elected for 1934: Past Chairman, G. H. Ferguson, Ottawa; Chairman, T. J. Lafrenière, Montreal; Vice-Chairman, M. Pequegnat, Kitchener; Trustees, N. J. Howard, Toronto, and R. H. Murray, Regina; and Secretary, A. E. Berry.

The second day of the convention brought a joint session with the health officers, a feature of which was a symposium on "Sanitation in Processing," with the following papers: "Slaughter Houses," by Dr. A. R. B. Richmond, Toronto; "Ice Cream Plants," by Mr. T. J. Lafrenière, Montreal; "Cheese Factories and Creameries," by Mr. A. V. Delaporte, Toronto; and "Soft Drink Bottling Plants," by Mr. G. A. H. Burn, Toronto. This was preceded by "Engineering Aspects of Milk

Control," by Dr. A. E. Berry and the final paper on the morning programme was "Dangers in Cross-connections in Plumbing," given by Mr. Ferguson. The only engineering paper in the afternoon was one given by Mr. N. MacNicol, Commissioner of Works for Forest Hill Village, on "Smoke

Abatement." The meetings attracted a great deal of interest and showed the growth of the Section since its recent formation. It has been encouraging to find the engineers of Canada taking their place in public health advancement.

Canadian Institute on Sewage and Sanitation

A FURTHER step has been taken to complete the organization inaugurated some time ago in Canada and brought about to deal chiefly with sewerage projects. The executive met to draft a constitution and to agree upon other details. The name of the organization was announced as the "Canadian Institute on Sewage and Sanitation." This is a purely Canadian group, and includes the entire Dominion. Affiliation has been made

with the Federation of Sewage Works Association in the United States. This will enable the members to secure the Journal published by that Association. A campaign for membership in the Institute will be initiated at once. There appears to be a real opportunity in Canada for this new organization in the field of sanitation and it is expected that representation from all parts of Canada will be found soon in the membership list.

NEWS NOTES

Annual Congress Royal Sanitary Institute

THE Royal Sanitary Institute will hold its annual congress at Blackpool from June 17th to 24th. Practically every branch of public health and sanitation will receive attention, and in addition there will be a health exhibition illustrating various products and appliances which aim at improving the public health.

Alberta

THE medical service which has been provided by the provincial Department of Health in the Wanham district has been discontinued. Dr. Margaret Owens, who has been in charge of the district, has been appointed to Notikewin.

Miss C. Deane has been appointed to the staff of the Red Deer Full Time Health District.

Saskatchewan

A MARRIAGE act recently passed by the Legislature requires one of the parties to the prospective union—the male—to produce a medical certificate of freedom from certain physical and mental diseases. While the effect of the present legislation on racial improvement may not be great, it indicates that the people's representatives are thinking along channels which eventually may lead to compulsory sterilization of the unfit.

During the year 1932 the total cost of waterworks systems approved by

the provincial department of public health was \$447,009.34, while the cost of sewage and sewage disposal systems approved under the Public Health Act was \$406,568.36. The greater part of this expenditure was made by the larger urban municipalities in extending sources of water supply and domestic and storm sewerage systems. The city of Regina completed the construction of a ten-million-gallon reinforced concrete reservoir and developed the Mound Springs area to the north of the city with a view to augmenting the city's water supply.

Manitoba

THE Department of Health and Public Welfare is promoting a plan for the safeguarding of the milk supplies of small towns. The plan, which already has been accepted by fourteen towns, requires that the milk be from tuberculin-tested cows, that it be produced and maintained under clean conditions and delivered in properly sterilized bottles. The work is carried on under the supervision of the provincial Director of Food Control, thereby relieving the local health officer of much of the onus that at times is irksome to a physician in general practice.

Miss Anna E. Wells, director of the Division of Health Education, will attend the Congress of the International Council of Nurses which is being held in Paris and Brussels from July 9th to 14th. Miss Wells will present a paper on "The Relation between the Teacher and the School Nurse" before the School Nursing Section.

Ontario

SIX physicians have been awarded the Diploma in Public Health at the School of Hygiene, University of Toronto: Dr. F. J. Tourangeau, Dr. J. A. Lapierre and Dr. E. Martel, Quebec; Dr. C. W. MacMillan, Saint John, N.B.; Dr. A. Roy, St. Jean Baptiste, Man.; and Dr. A. H. Sellers, Toronto. Dr. Martel and Dr. Sellers are taking the summer course in field work. Dr. S. S. Murray, Vancouver, and Dr. H. A. Ansley, Thessalon, Ont., have successfully completed the work of the first term.

"Damaged Lives," a talking picture dealing with the evils of social diseases, had its first showings on the continent at the Tivoli Theatre, Toronto, on May 22nd, when it opened an indefinite engagement under the auspices of the Canadian Social Hygiene Council. The picture was produced in Hollywood under the supervision of Dr. Gordon Bates, General Director of the Council, which shortly will sponsor showings in other Canadian cities. It is expected that the picture will be shown later throughout the British Empire and in the United States and other foreign countries, having everywhere the sponsorship of the Council.

Quebec

THE annual meeting of the medical officers of the Provincial Bureau of Health was held in Quebec on May 30th, 31st and June 1st. As in past years, the conference was featured by round table discussions.

COLONEL LORNE DRUM

COLONEL Lorne Drum, Director-General of the Saint John Ambulance Brigade, died suddenly on April 15, 1933, at the age of 62. Colonel Drum had a distinguished record during the Great War and was a most efficient officer. During the early years of the War he was in charge of No. 3 (McGill) Canadian Military Hospital at Boulogne, France. Since then he had been stationed at a number of military district headquarters in Canada and for the past thirteen years had served as medical officer for Military District No. 11 at Victoria. Retiring from the service in 1932, he was selected to succeed Colonel Hodgetts as head of the Saint John Ambulance Association in Canada.

Colonel Drum was one of the founders of the Canadian Public Health Association, having taken an active part in the early work of the Association. For several years he occupied the position of Honorary Secretary. His many friends in the organization and throughout Canada learned with the greatest regret of his passing. To Mrs. Drum and to her son the Association extends its deep sympathy.

BOOKS AND REPORTS

Psychology and Psychiatry in Pediatrics: The Problem. *The Report of the Subcommittee on Psychology, The White House Conference on Child Health and Protection.* Published by The Century Co., 353 Fourth Avenue, New York, 1932. 146 pages. Price, \$1.50.

This volume is a report of the subcommittee on psychology and psychiatry, of which Bronson Crothers, M.D., Assistant Professor of Pediatrics, Harvard University Medical School, is chairman. Six additional physicians and one doctor of philosophy comprise the subcommittee, which is representative of acknowledged experts in the field of psychiatry and mental hygiene.

The scope of the investigation is clearly set out, namely, an enquiry into those aspects of the subject which are of direct interest to the physicians in charge of the mental care of children. In the introduction certain definitions are given which definitely state the point of view of the committee, and incidentally keep the reader on firm, or moderately firm ground.

A very interesting table is presented, showing the results of a survey of some 64 Class A medical schools in reference to the time devoted to psychiatry. The subcommittee acknowledges that these figures are surprising and disconcerting. No one will disagree with the conclusion that adequate medical care of the child cannot be given without intelligent attention to the intellectual and emotional difficulties which may obviously present themselves. The adviser should be the well informed physician, the "psychiatrally intelligent and educationally sensitive doctor who should be qualified by his medical training to deal adequately and successfully with most of the problems of this nature."

The extracts from discussions by experts make excellent reading. Approximately half of the book is devoted to an outline of the programmes of child guidance groups in which section the reader finds the going heavy unless he is acutely interested in this phase of the subject. The report of the subcommittee is well done and states adequately the problem which it has set out to clarify. D.T.F.

Public Health Organization. *Report of the Committee on Public Health Organization, E. L. Bishop, M.D., chairman. A publication of the White House Conference on Child Health and Protection. Published by the Century Co., 353 Fourth Avenue, New York, and London, 1932. 345 pages. Price, \$3.00.*

The report discusses the existing organization for public health, federal, state, urban and rural, as well as that of non-official bodies, in the United States, briefly traces their history and offers suggestions for improvements designed to meet the public health needs of the present day.

Public health, the report points out, is no longer concerned primarily with the prevention of disease; to-day public programmes are expected actively to promote mental and physical health as well as to prevent disease. This change in public health is creating a demand for more complete and efficient organization; it necessitates the closest co-operation between official and voluntary public health bodies.

In addition to discussion of the administration problems and relation of the various units of public health service from the federal organization to the rural, other important questions, such as the training of personnel, administration of child health work, relation of medical practitioners and dentists to health programmes, the health aspect of food control and research, are taken up.

The county health unit is recommended for rural areas and both there and in urban communities the only satisfactory service is that of the whole-time trained health officer to direct the work. One views with satisfaction the strong plea made for the employment in many health activities of the practising physician. In child health, for example, the family doctor should become a practitioner of preventive as well as of curative medicine.

There should be no political preference for employees and the salaries should be on a scale to attract satisfactory results.

Attention is called to the very powerful non-official public health organizations in the United States. There are many wealthy foundations devoted in whole or in part to the promotion of health. There are societies for the promotion of almost every known public health activity. These organizations may briefly be grouped under the heads of: social foundations, national associations, local associations (affiliated or not with national), life insurance companies, and commercial groups.

The report points out that in order to make non-official participation in public health fruitful, four general principles should be adopted:

1. The local health officer must be made directly responsible for the health of his district.
2. Each function in the area should be performed by the agency best qualified therefor.
3. The non-official agencies in a given community should form a common health council under the chairmanship of the health officer.
4. The health officer should establish permanent contacts through memberships on non-official boards.

It is recommended that departments of hygiene and preventive medicine should be established for the training of personnel, and that medical schools should set up post-graduate training of physicians and nurses.

Nothing very new is recorded, but the volume forms a convenient summary of the scope and organization of the agencies engaged in public health work in the United States and should, in this way, prove useful to the student and the public health officer.

J. W. S. McC.

The Baby. *A publication of the Department of Health of Ontario, 1933. 64 pages.*

This book, with its bright cover and easily read contents, is a welcome relief from the usual government blue book publication. It is scientifically accurate and practical and contains a fund of information for expectant and young mothers.

In chronological order it discusses prenatal care of the infant and infant feeding, as well as the care of the runabout child. Registration of the

baby's birth and immunization against various diseases are strongly urged. An interesting and unique folder illustrates the correct way to bathe and clothe the baby.

The book is heartily recommended and should be placed in the hands of all expectant mothers. Copies may be obtained free of charge from the Provincial Department of Health of Ontario, Parliament Buildings, Toronto 5, or from local health officers in Ontario.

R. R. McC.

REPORTED CASES OF CERTAIN COMMUNICABLE DISEASES IN CANADA*
BY PROVINCES

MARCH, 1933

Diseases	P.E.I.	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Diphtheria.....	—	1	4	79	47	23	19	—	—
Scarlet Fever.....	—	45	54	266	299	91	75	17	39
Measles.....	10	49	18	536	1106	5	18	16	55
Whooping Cough.....	—	2	1	540	513	125	55	11	94
German Measles.....	—	15	—	26	9	1	2	—	28
Mumps.....	—	16	—	400	1006	151	38	—	86
Smallpox.....	—	—	—	—	5	—	14	—	—
Cerebrospinal Meningitis.....	1	1	—	3	1	1	1	—	—
Anterior Poliomyelitis.....	—	—	1	3	1	—	—	—	1
Typhoid Fever.....	—	—	6	49	20	7	—	—	3
Trachoma.....	—	—	—	—	2	—	1	—	6

APRIL, 1933

Diseases	P.E.I.	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Diphtheria.....	—	11	7	97	59	22	18	1	7
Scarlet Fever.....	1	38	13	276	384	85	77	23	17
Measles.....	54	41	38	911	944	33	5	30	10
Whooping Cough.....	—	3	—	326	480	148	45	15	62
German Measles.....	—	22	—	60	76	1	3	—	32
Mumps.....	—	8	—	409	1113	173	34	—	145
Smallpox.....	—	—	—	—	3	—	2	—	6
Cerebrospinal Meningitis.....	—	2	1	4	6	1	2	2	2
Anterior Poliomyelitis.....	—	—	—	6	1	—	—	—	—
Typhoid Fever.....	1	—	10	68	36	5	—	4	9
Trachoma.....	—	—	—	—	—	—	10	—	9

*Data furnished by the Dominion Bureau of Statistics, Ottawa.

CURRENT HEALTH LITERATURE

These brief abstracts are intended to direct attention to some articles in various journals which have been published during the preceding month. The Secretary of the Editorial Board is pleased to mail any of the journals referred to so that the abstracted article may be read in its entirety. No charge is made for this service. Prompt return (after three days) is requested in order that the journals may be available to other readers.

Causes of Illness in 9,000 Families, Based on Nation-wide Periodic Canvasses, 1928-1931

The survey which forms the subject of this report covered 8,758 families in 130 localities in 18 states. Each family was observed for period of 12 consecutive months, being visited at intervals of 2 to 4 months to obtain the sickness record. The data are therefore the most extensive now available, dealing with illnesses of all kinds in a fairly representative general population group.

An illness rate of 850 per 1,000 persons was found. Illnesses that caused loss of time from work, school or other occupation amounted to 516 per 1,000 persons, while illness in which the patient was confined to bed for one or more days amounted to 434 per 1,000 persons. Minor respiratory conditions were the most frequent causes of illness. The rate for respiratory diseases was 345 per 1,000; for diseases of the digestive system, 85.9 per 1,000; and for accidents and other external causes, 73.7 per 1,000. For all other broad groups of causes the incidence was less than 40 per 1,000.

Selwyn D. Collins, Pub. Health Rep., 48: 283 (March 24), 1933.

Lead Poisoning from the Burning of Battery Casings

This report deals with a group of forty cases of acute lead poisoning which occurred in Baltimore. The cases occurred in poor Negro families where discarded storage battery casings had been used as fuel. The casings carried a considerable deposit of lead salts and the burning of them in defective stoves permitted the escape of lead fumes. Intensity of exposure rather than duration seems to have been chiefly responsible for the cases. Control measures were instituted and have apparently eliminated this health hazard in Baltimore. More recently, similar situations have occurred in Detroit and elsewhere.

Williams, Schulze, Rothchild, Brown and Smith, J.A.M.A., 100: 1485 (May 13), 1933.

Does a Primary Tuberculous Infection Afford Adequate Protection Against Consumption?

From observations on 84 children, covering periods up to ten years, the following conclusions are reached by the author. Primary

tuberculous infections, far from producing any immunity, are distinctly detrimental. Primary infection so alters the normal resistance in such a manner that, instead of again being able to experience the benign primary type of tuberculosis, the patient is doomed to develop consumption if successfully reinfected from exogenous or endogenous sources. Active immunization against tuberculosis with attenuated bacilli may not be a safe procedure if this method duplicates the immunological changes that accidental human contact infection produces.

Chester A. Stewart, J.A.M.A., 100:1077 (Apr. 8), 1933.

Diphtheria Immunization with a Single Injection of Precipitated Toxoid

To toxoid, prepared in the usual manner with formaldehyde, alum was added until precipitation was complete. Tests in guinea pigs indicated that the washed precipitate produced a high degree of immunity and a single injection (15 to 10 units) has been given to a total of 798 children. Of these, 185 were strongly Schick positive before injection and 171 were found to be Schick negative two to six months later. The original immunity status of the other 613 children was not known, but 72 per cent were pre-school children and 96.6 per cent were Schick negative when tested two to four months later.

A. H. Graham, L. R. Murphree and D. G. Gill, J.A.M.A., 100:1096 (Apr. 8), 1933.

The Pellagra-Preventive Value of Autoclaved Dried Yeast, Canned Flaked Haddock and Canned Green Peas

In previous papers the author described a basic diet meeting all physiological requirements except in that it was deficient in pellagra-preventive vitamins and which leads to the production of pellagra in three to six months. State hospital patients were placed on this diet and the pellagra-preventive value of dried baker's yeast and canned green peas was investigated. The yeast was found to be a good source of the pellagra-preventive factor, retaining its potency in spite of autoclaving at 15 lbs. for 7½ hrs. Canned green peas also supply the factor and provide a convenient source of this essential in pellagriferous sections during the spring months when pellagra-preventive supplements are scarce.

G. A. Wheeler, Pub. Health Rep., 48:67 (Jan. 20), 1933.

